DELAWARE STATE MEDICAL JOURNAL

Official Organ of the Medical Society of Delaware

INCORPORATED 1789

VOLUME 32 | JANUARY, 1960 | NUMBER 1

RHEUMATOID ARTHRITIS IN CHILDHOOD;

INVOLVEMENT OF THE HIP

IN EPILEPSY... PREREQUISITE FOR PARTICIPATION: THERAPY

With the use of medications, epileptic students may be enabled to participate in many of the same activities as other students.[1]

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for control of grand mal and psychomotor seizures

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KAPSEALS® "In the last 15 years several new anticonvulsant agents have come into clinical use but they have not replaced diphenylhydantoin [DILANTIN] as the most effective single agent for a variety of reasons. Most of them are less effective in control of seizures, have a greater sedative effect and higher incidence of sensitivity reactions."[2]

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KAPSEALS When it has been demonstrated that the combination of Dilantin and phenobarbital is helpful in a patient and that these drugs are well tolerated, the use of PHELANTIN, a capsule providing both drugs, is often a great morale builder because it enables the physician to reduce the total number of pills or capsules the patient is required to take. It is less expensive medication and it prevents the patient from manipulating the dosage.[3] PHELANTIN also contains methamphetamine (desoxyephedrine) to minimize the sedative effect of phenobarbital.

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CELONTIN Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

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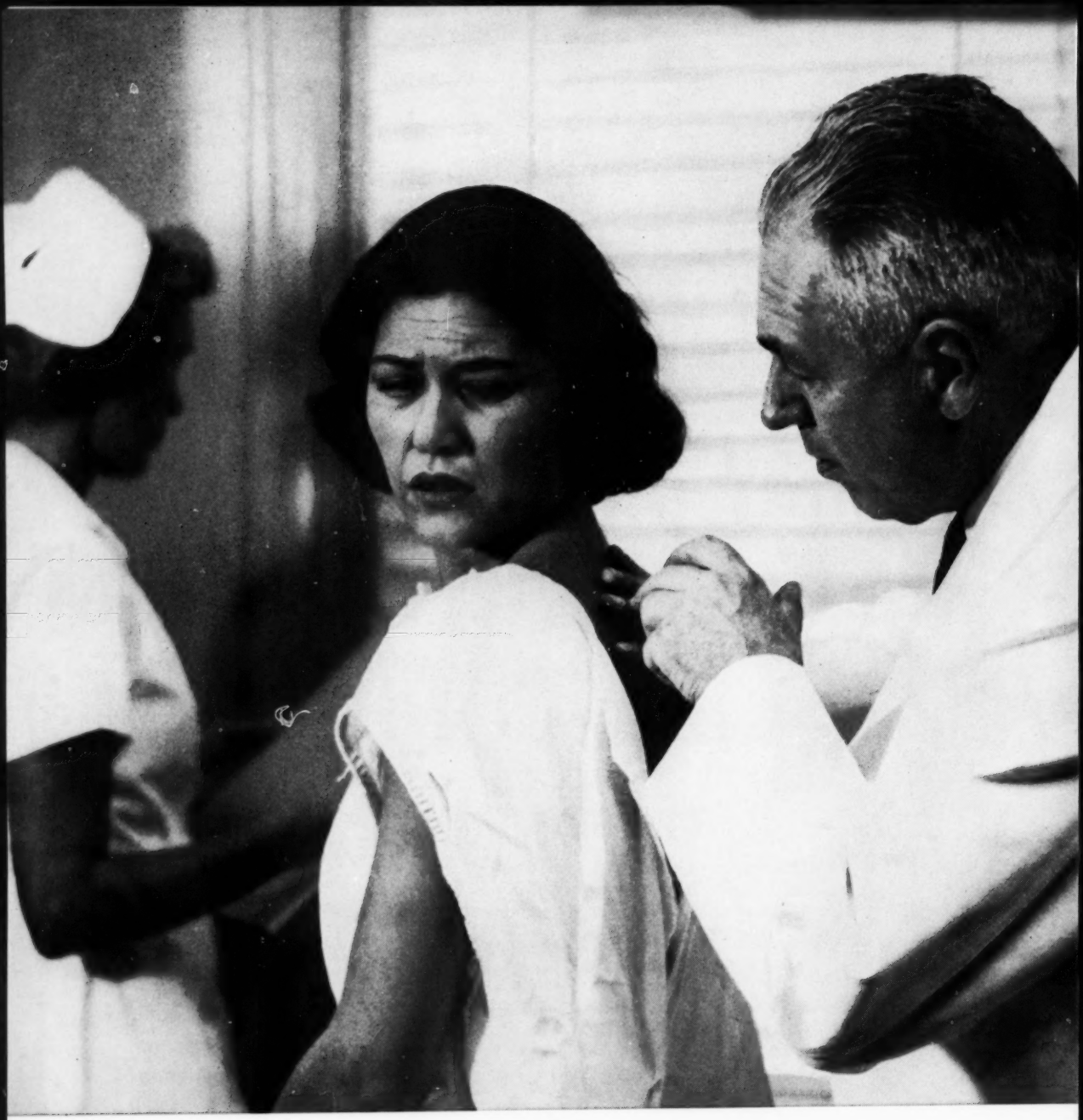

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and

11. Laughlin, H. P.: The Neuroses in Clinical Practice, Saunders, Philadelphia, 1956, pp. 448-481.

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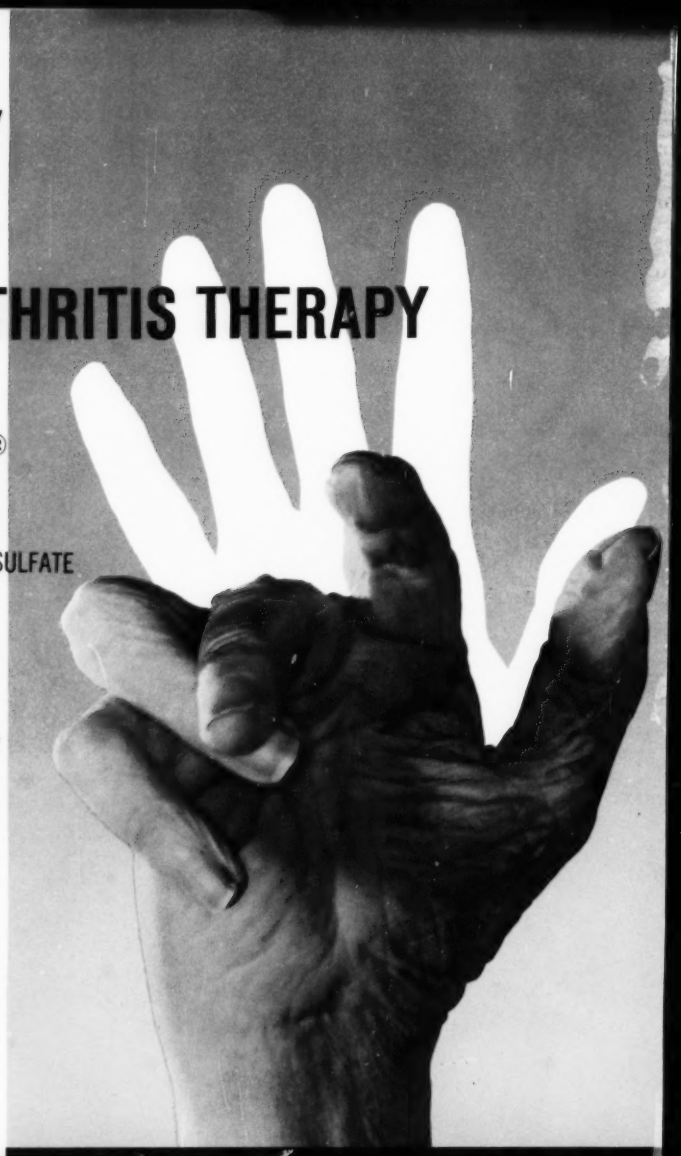

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Bagnall, A. W. (Univ. British Columbia, Vancouver, B.C.): A.M.A. Clinical Meeting (Scientific Section, Exhibit No. 124), Minneapolis, Minnesota, Dec. 2-5, 1958.

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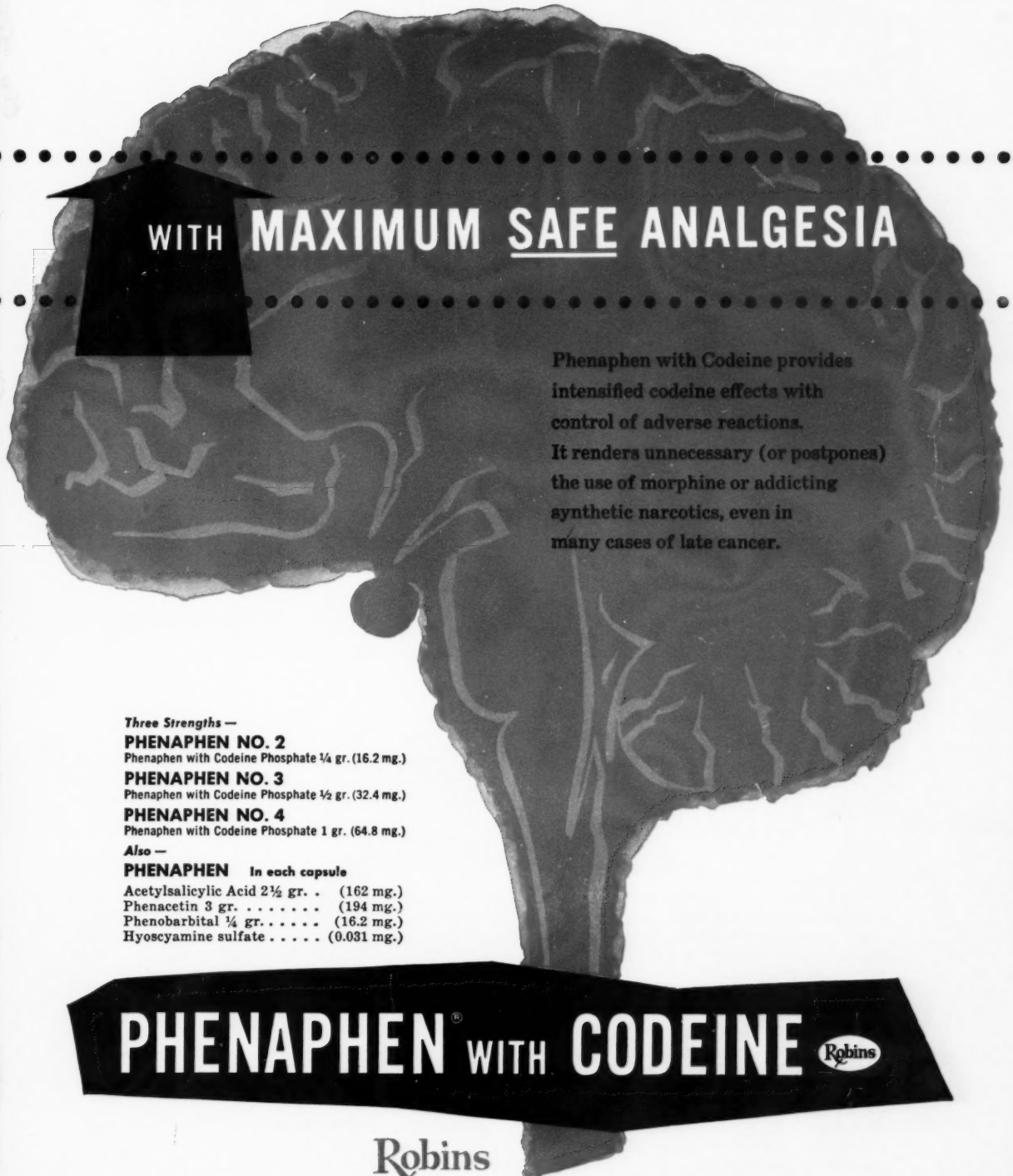

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Miller, R. F.: Clin. Rev. 1:10 (July) 1958

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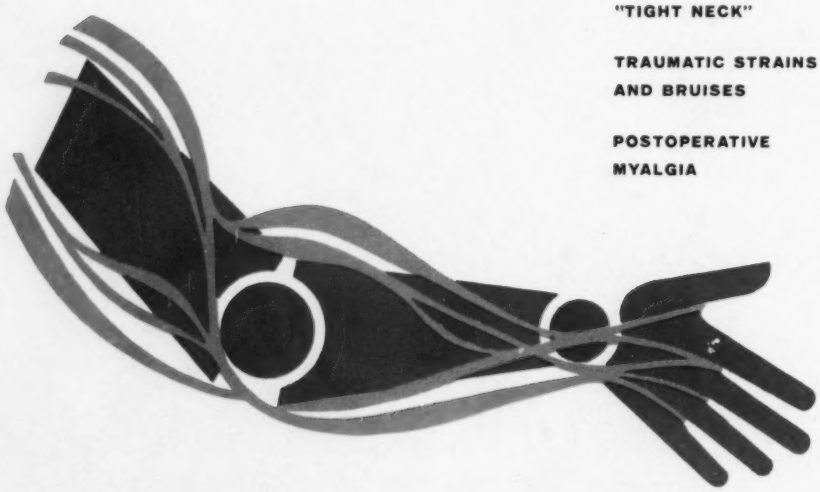

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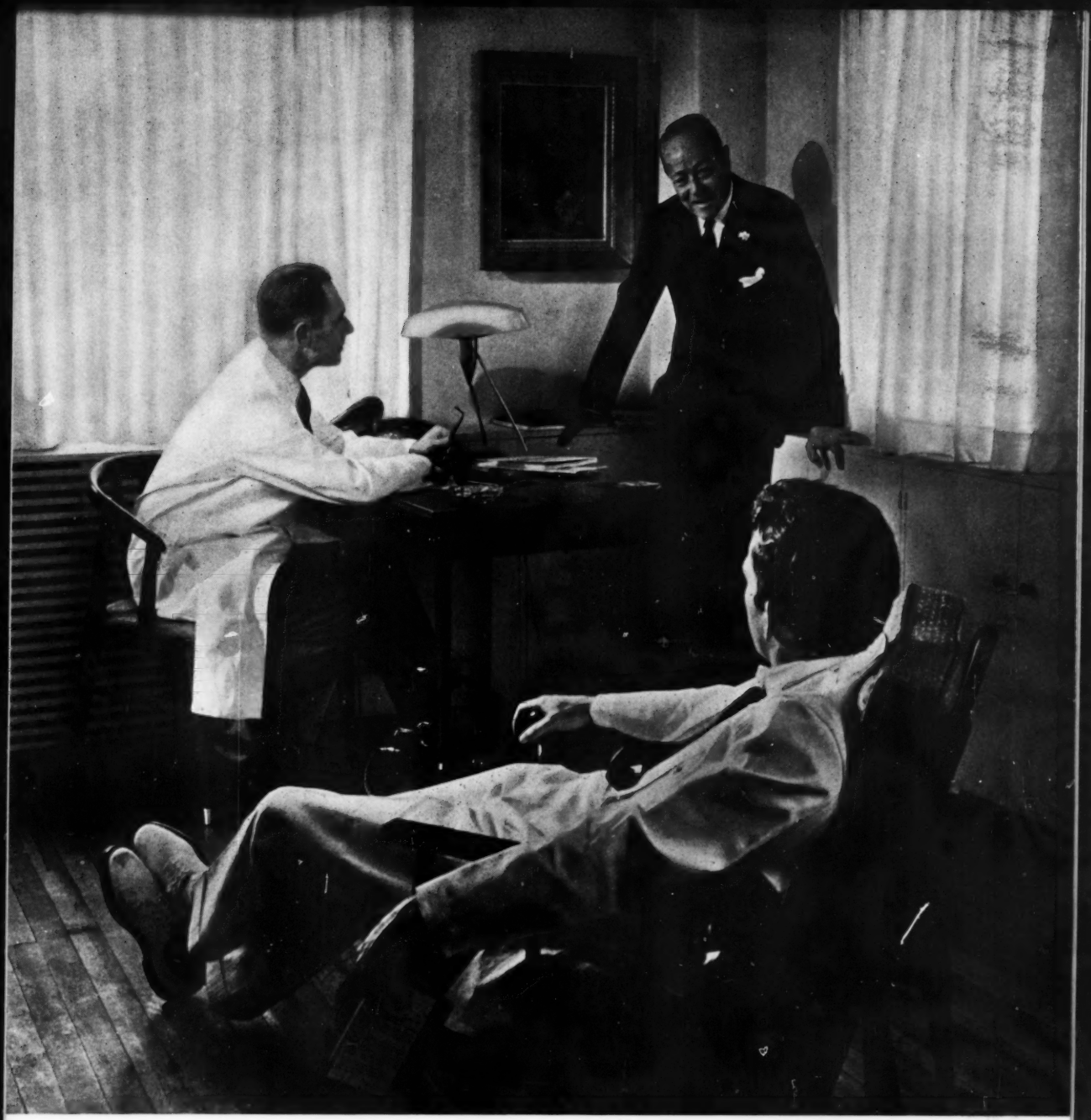

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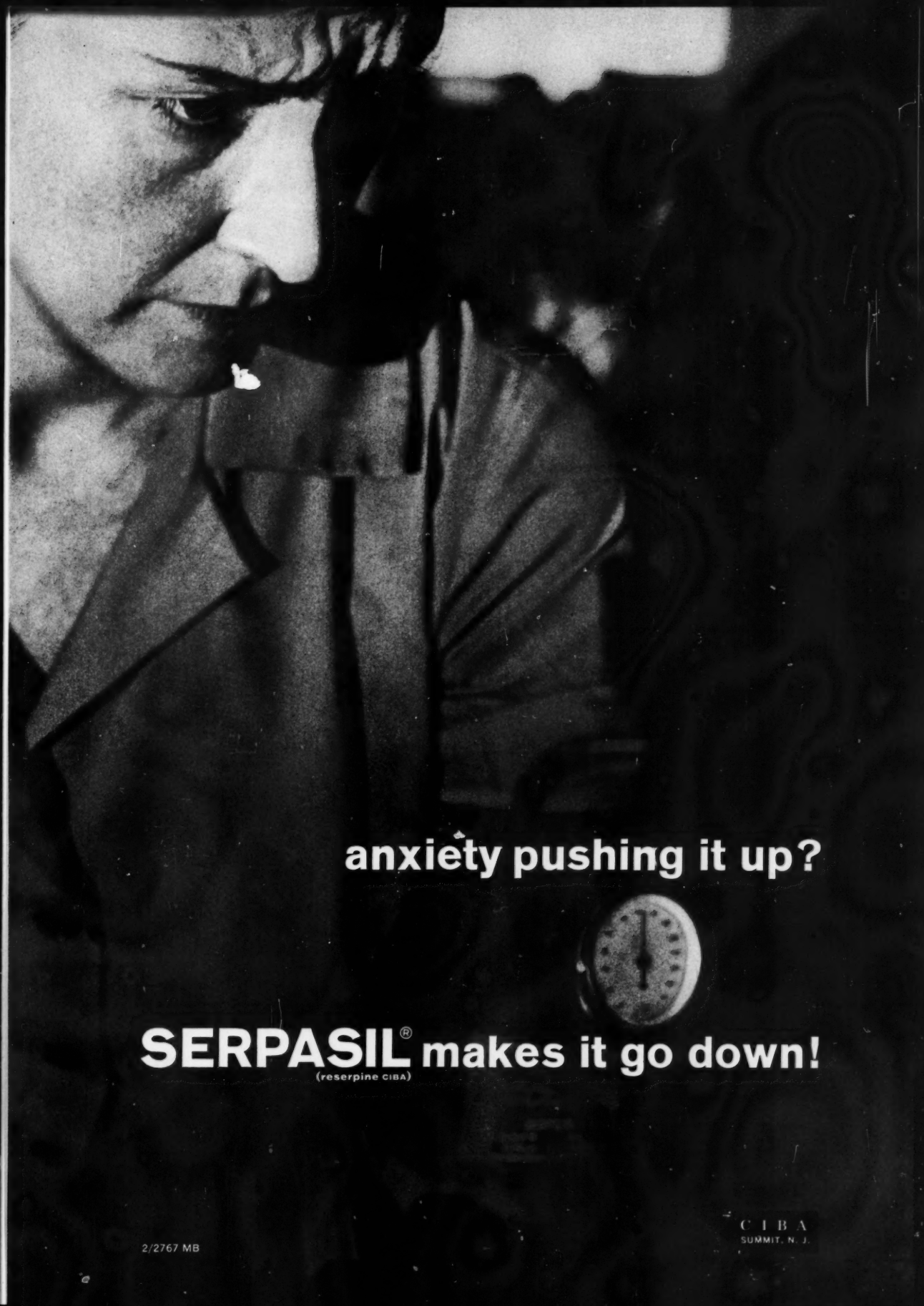
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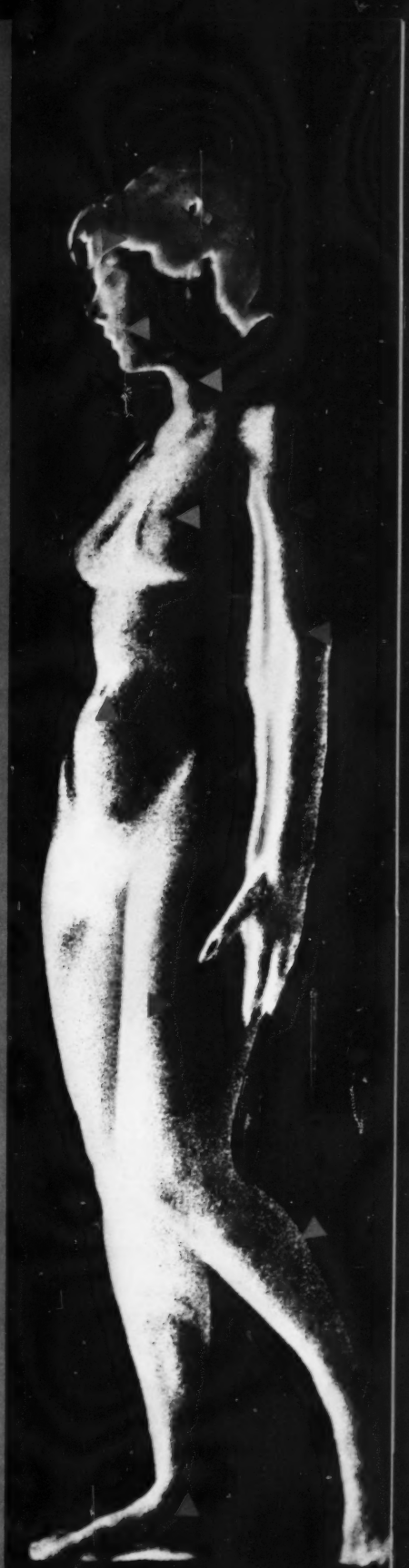

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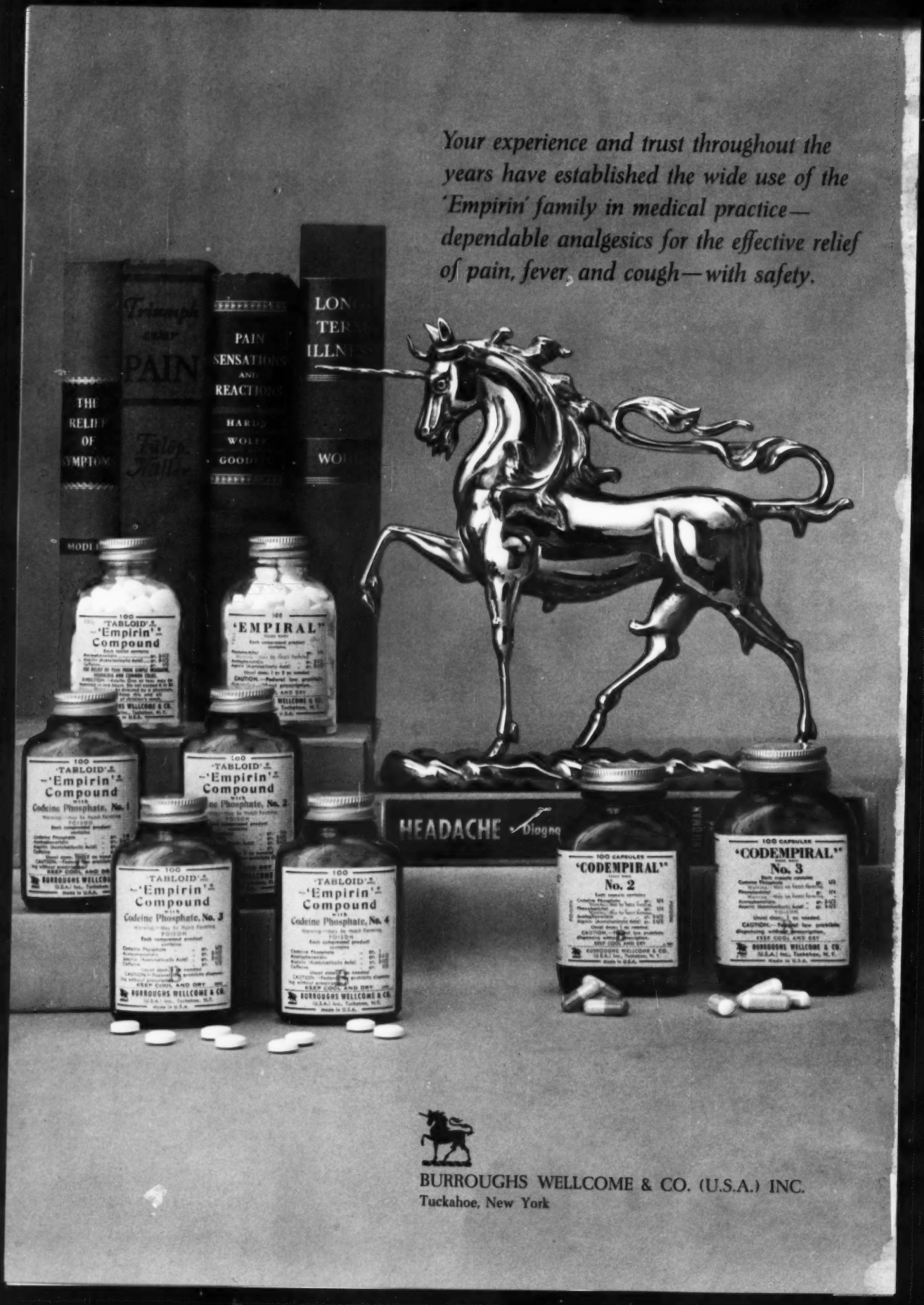
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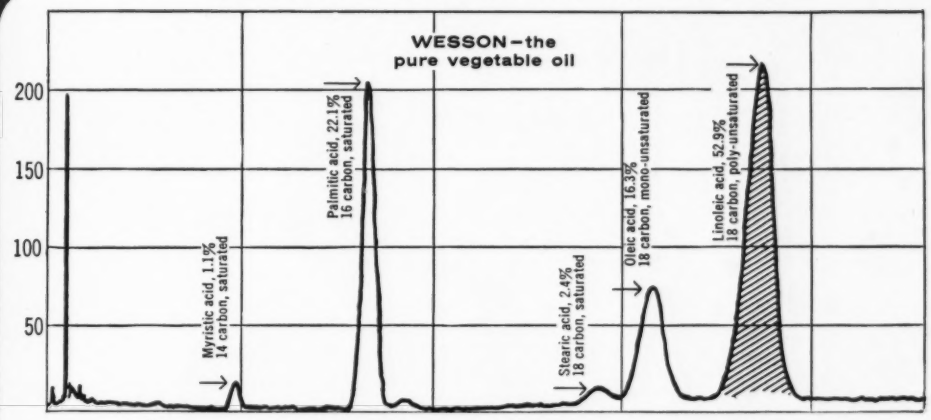

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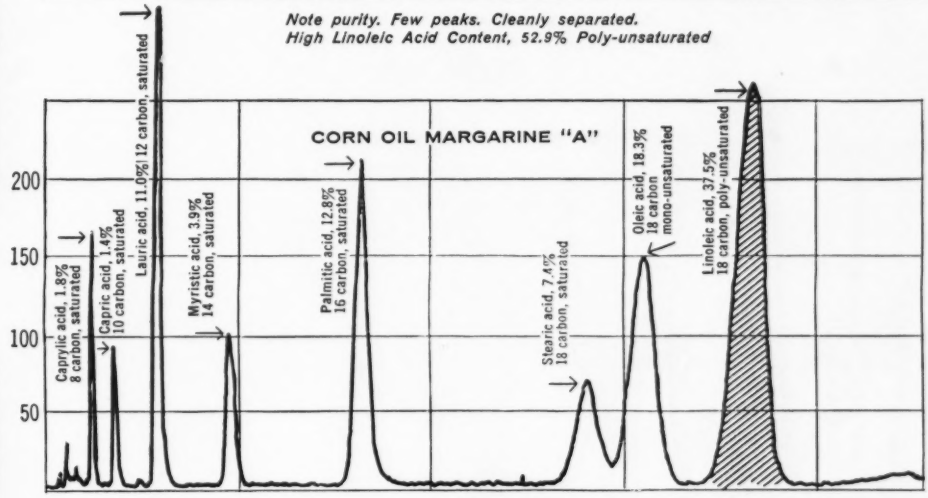

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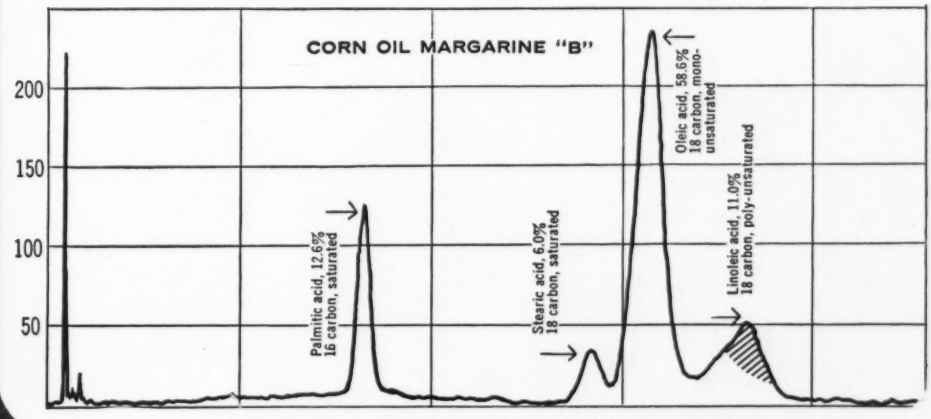

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(Hirsch, H. A. and Finland, M.: Antibacterial Activity of Serum of Normal Subjects after Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. *New England J. Med.* 260:1099 (May 28) 1959.)

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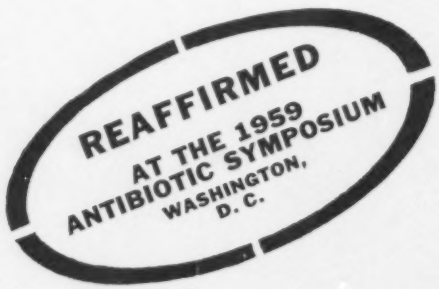

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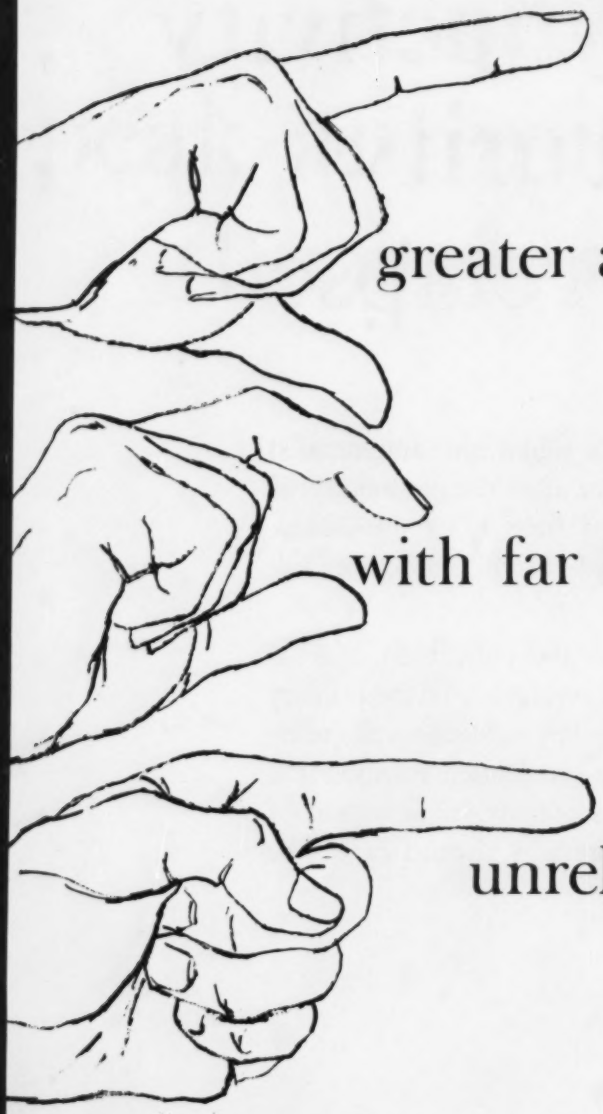

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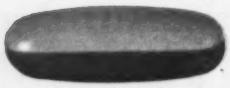

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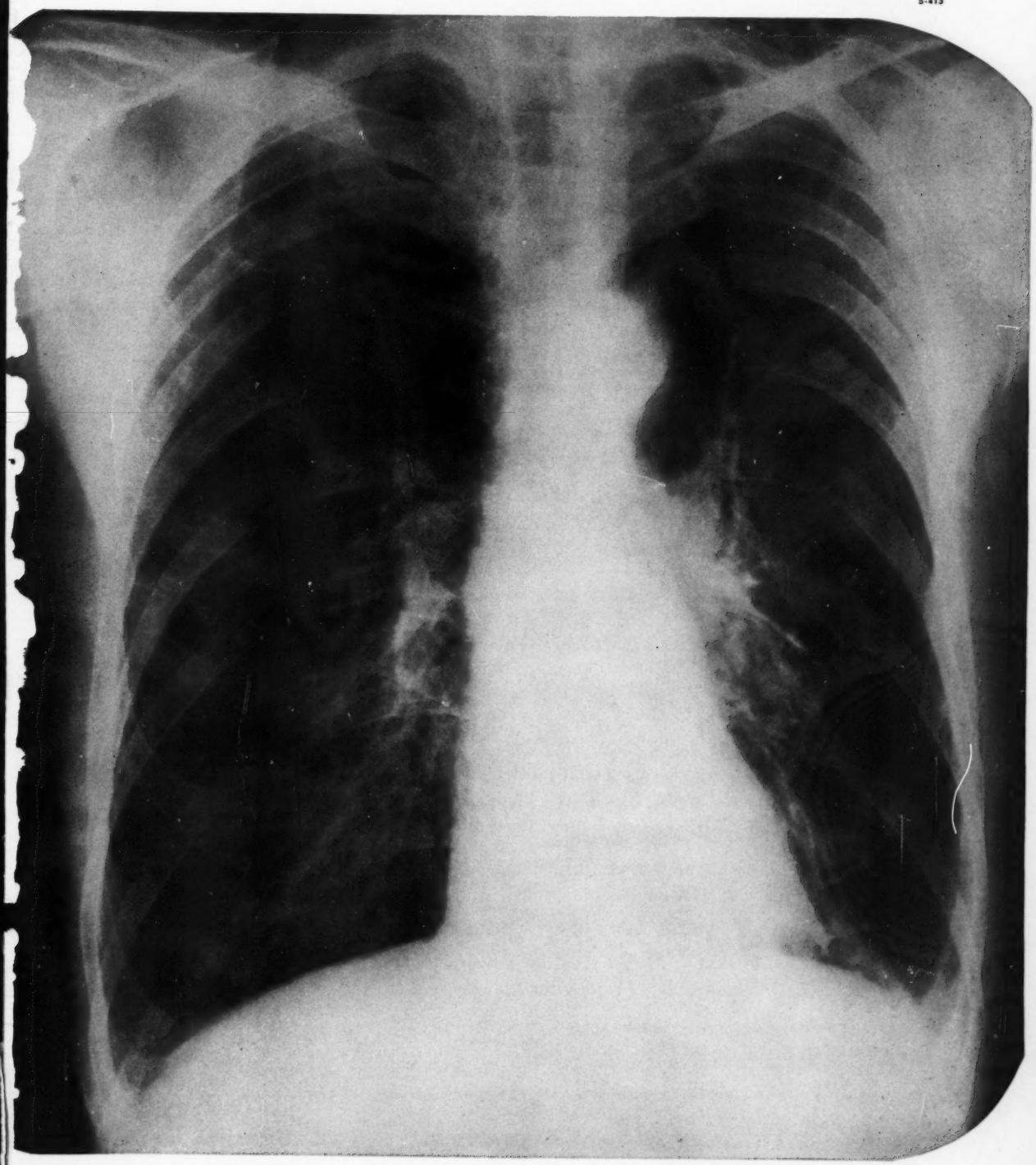

DELAWARE STATE MEDICAL JOURNAL

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RHEUMATOID ARTHRITIS IN CHILDHOOD;*

INVOLVEMENT OF THE HIP

● **This analysis of thirty-five cases and eight brief case reports of rheumatoid arthritis in children, from the Alfred I. duPont Institute, points to a ratio of girls to boys as six to one; the average age of onset as five years; the knee as the first joint most frequently involved and that 57% of the children became severely disabled.**

A. R. SHANDS, JR., M.D.

C. C. MUEHE, M.D.

In a total of 6,388 children seen for the first time at the Alfred I. duPont Institute in Wilmington, Delaware, rheumatoid arthritis of one or more joints was found in thirty-five cases; this is an incidence of one in every 183 children examined in the clinic and one in every 1865 children admitted to the wards (Table I). Eleven of these had no hip involvement. The hip joint was affected primarily in only one child.

Affections of the hip in childhood are quite common in orthopaedic clinics, but few are due to rheumatoid arthritis. In our clinic, over an eighteen-year period, while there were twenty-four children with hip joint involvement associated with rheumatoid arthritis 937 or 14.7 per cent of all children examined had a diagnosis of a hip joint affection. The number of rheumatoid arthritic hip children represents 2.6 per cent of the total hip cases. Of the hip affections, congenital dislocation, congenital acetabular dysplasia, coxa plana, and a slipping of the upper femoral epiphysis were the most common.

In all series of cases of rheumatoid arthritis, both juvenile as well as adult, there is an overwhelming predominance of the female over the male. In a series of juvenile cases reported in 1946 by Coss and Boots[1] at the Presbyterian Medical Center in New York City, the ratio of female to male was five to one, while in a series of nineteen children reported by Clemmensen and Arnso[2] from the Municipal Hospital in

*Presented in a Symposium on the Hip at the meeting of the American College of Surgeons, Chicago, Illinois, on October 8, 1958.

**Alfred I. duPont Institute, Wilmington, Delaware.

Copenhagen, the ratio was four to one. In our series there were thirty girls and five boys, or a six to one ratio (Table II). In the thirty-five cases there was only one Negro child (2.9 per cent), although the incidence of the Negro patients in the admissions to the hospital is approximately 15 per cent.

The average age of thirty-five patients when first seen was nine years seven months, varying from two to sixteen and one-half years (Table III). The average age of onset, however, was five years, varying from six months to thirteen years. There were only five of the thirty-five, or 14 per cent, in whom the age of onset was over eight years; in seventeen, org 49 per cent, the age of onset was four years or less, so it can definitely be said that in our series this disease occurs more often in the young child of the preschool and early school age periods. In the literature there are few references to the age of onset.

Short, Bauer and Reynolds[3] have stated that the knee joint is most commonly involved first and, next, the joints of the hands and feet. Lockie and Norcross[4] and Edstrom[5] found that rheumatoid arthritis in childhood starts more often in the larger joints than in the smaller joints. These findings are confirmed in our series (Table IV). There were only two monarticular involvements, one knee and one elbow, or

TABLE I

STATISTICS ON
RHEUMATOID ARTHRITIS (R.A.)
AT THE ALFRED I. duPONT INSTITUTE
JULY 1940 — OCTOBER 1958

	No.	Per Cent
New Patients in Clinic	6388	
With R. A.	35	.55 (1 in 183)
Plus Hip Involvement	24	.37
Admissions to Ward	1865	
With R. A.	32	1.72 (1 in 58)
Plus Hip Involvement	24	1.29

TABLE II

SEX INCIDENCE

	No.	Per Cent
Girls	30	86
Boys	5	14
	35	

Ratio — Girls: Boys — 6:1

TABLE III

AGE OF ONSET AND AGE
AT FIRST EXAMINATION

	Of Onset	At First Examination
6 mos. - 2 yrs.	5	0
2 yrs. - 3 yrs.	6	3
3 yrs. - 4 yrs.	5	2
4 yrs. - 8 yrs.	9	8
8 yrs. - 12 yrs.	8	7
12 yrs. - 15 yrs.	2	11
15 yrs. and over	0	4
	35	35

TABLE IV

INITIAL JOINT INVOLVEMENT

Knee	13
Wrist	5
Hand	4
Ankle	4
Elbow	3
Foot	2
Neck	1
Hip	1
Multiple	2
	35

TABLE V

DEGREE OF SEVERITY

	No.	Per Cent
1. Mild	4	11
2. Moderate	11	31
3. Severe	20	57
	35	

TABLE VI

ROENTGENOLOGIC CHANGES IN 24 HIP CASES WITH RHEUMATOID ARTHRITIS

	No.	Per Cent
1. Decalcification	19	79
2. Bone Destruction	9	38
3. Bone Proliferation	11	46
4. Narrowing of Joint Space	17	71
5. Deformity of Pelvis	10	42
6. Head of Femur		
a) Hyperplasia	15	63
b) Hypoplasia	5	21
c) Subluxation or Luxation	8	33
7. Sacroiliac Involvement	13	54
8. Symphysis Pubis Involvement	6	25

6 per cent of the total in the thirty-five cases.

Concerning the severity and extent of crippling in the thirty-five cases, twenty (57 per cent) could be classified as severely disabled, i.e., those who had multiple joint involvement, contractures, difficulty in walking and carrying on the activities of daily living; eleven (31 per cent) were moderately disabled, and four (11 per cent) were only mildly involved (Table V). The per cent of severely disabled children with rheumatoid arthritis seen in a crippled children's hospital is undoubtedly greater than would be seen in an arthritis clinic of all ages. Most of the children usually have been either on a children's ward in a general hospital or in a children's hospital for long periods of time before their admission to a crippled children's institution.

The roentgenologic changes of the skeleton which have been most frequently reported[1,6] are decalcification, bone production, bone destruction, narrowing of the joint space, ankylosis, deformities of the head of the femur, and varying degrees of luxation. Decalcification, narrowing of the joint space, and hyperplasia of the head of the femur are the three most common roentgenologic findings in our series (Table VI).

The following are brief case reports on the eight children whose roentgenograms represent the most severe, and at the same time the most typical hip joint changes:

Case No. 1 is a five and two-third year old white girl, admitted to the Alfred I. duPont Institute in June, 1946. The past history shows that at the age of four and one-half years she fell and injured her right knee which became swollen; this was followed by a persistent fever and transient migratory swelling of other joints. A diagnosis of rheumatic fever was made.

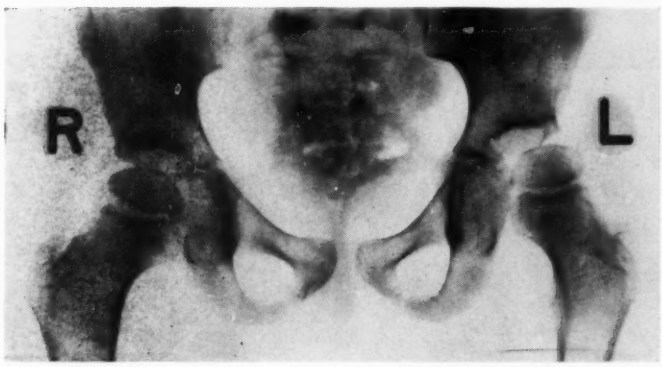


Figure 1. Roentgenogram of hips in Case 1, (June 28, 1946). Age 5 2/3 years, one year following onset of generalized rheumatoid arthritis. Note the lateral protrusion of the left femoral head.

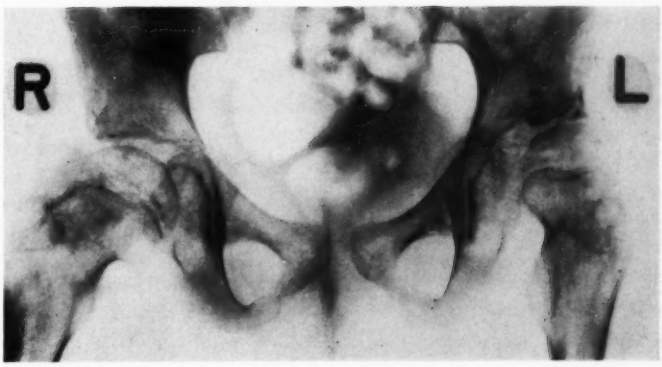


Figure 2. Roentgenogram of hips in Case 1, (9/1/48), two years and two months after Figure 1. Age 8 years. Note 1) a subluxation of the left hip, 2) irregularity and flattening of the superior margin of the left acetabulum, 3) enlarged femoral heads, 4) narrowing of the left femoral shaft, and 5) marked decalcification.

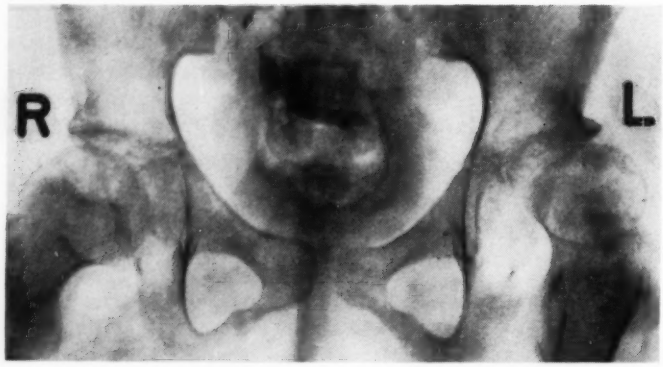


Figure 3. Roentenogram of hips in Case 1, (3/1/51), two and one-half years after Figure 2. Age 10 1/2 years Note 1) more marked subluxation of the left hip, 2) an upward angulation of the outer superior acetabular margin, and 3) marked decalcification. Both hips now have a flexion contracture of 25 degrees with little motion in either hip, especially the left.

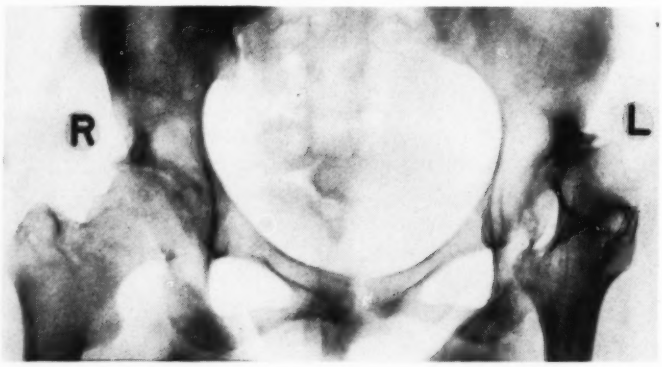


Figure 4. Roentgenogram of hips in Case 1, (9/20/56), five and one-half years after Figure 3. Age 16 years. Note 1) marked subluxation of the left hip, 2) shallow deformed left acetabulum with spur formation, 3) joint space on the right with shelf-like acetabular spur, and 4) deformity of both femoral heads, especially the left. Both hips had contractures of 30 degrees or more with a minimal amount of motion.

On admission there was swelling of the right knee and limited motion of the left hip. Roentgenograms of the hips showed a shallow acetabulum on the left with a beginning lateral protrusion of the head of the left femur (Fig. 1). Soon after admission a rapid and severe progression of involvement of all joints, except the shoulders, took place. Supportive medical treatment afforded some improvement early in her hospital course, only to be lost during subsequent exacerbations of her disease. These were initiated by several sever febrile episodes accompanying upper respiratory infections. Following the administration of folic acid, she developed a generalized dermatitis and a more marked joint involvement. In October, 1948, two years and two months following her first admission, the roentgenograms of the hips showed a definite subluxation of the head of the left femur with an irregular and shallow acetabulum (Fig. 2). She was discharged with limitation of motion in nearly all joints; however, she was able to walk for short distances with assistance.

One month after discharge, she was readmitted because of an acute and extensive dermatitis. Penicillin sensitive streptococci were cultured from the skin lesions. Penicillin therapy resulted in an immediate improvement in the dermatitis, but all joints remained stiff, including the jaws. Chest expansion was limited. There was now an increasing restriction of motion in both hips. Roentgen studies of the hips at this time showed marked decalcification, narrowing of both joint spaces, and a continued subluxation upward and outward of the left femoral head. Skin traction was not effective in reducing the subluxation. On discharge, seven and one-half months after admission, she was able to walk on crutches.

The third admission in July, 1949, one month after her second discharge, was again because of an acute exacerbation of the dermatitis. At this time there was practically no motion in the hips which were in 10 degrees flexion. In addition there was marked stiffening of all the other large joints of the extremities and of the fingers. The right knee was ankylosed in 120 degrees flexion. She was discharged four months after this admission.

The fourth admission in May, 1950, again was for treatment of her skin condition. At this time she went into cardiac failure. A questionable diagnosis of Rocky Mountain Spotted Fever was made on the basis of serologic studies. She responded to Aureomycin and was discharged in four months with the same stiffening in all major joints of the extremities, but still able to walk with the use of crutches.

For the next fifteen months while at home, her ability to ambulate on crutches and her general health definitely improved. In 1951 and in 1952 she was readmitted for two periods, one of six months and one of five months, for streoid therapy. Several courses of ACTH and Cortisone were given separately during these periods and which, associated with physical therapy, provided temporary improvement.

Roentgenograms of the left hip at the time of the sixth admission in 1952 showed a more marked subluxation with a shelf-like acetabular flattening and moderate epiphyseal deformity (Fig. 3).

She was readmitted for the seventh time in 1956, because of contractures, pain and stiffness in her hips. Motion had decreased in both hips until there was only a few degrees left. Roentgenograms of the hips now showed extreme narrowing of joint spaces, flattened deformed femoral heads, a moderate subluxation on the left with a flattened and irregular shelflike superior acetabular surface (Fig. 4). Traction, phys-

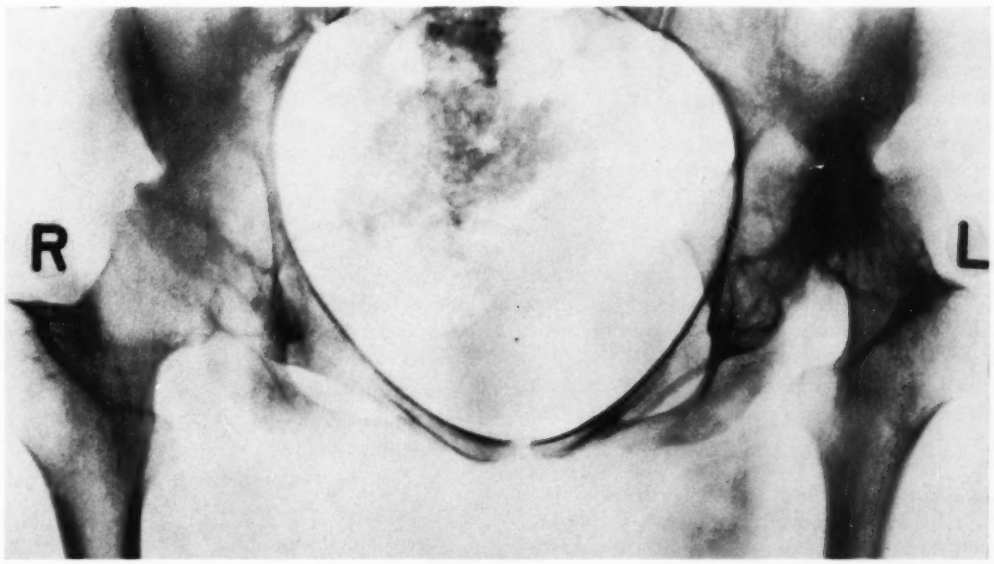


Figure 5. Roentgenogram of hips in Case 2, age 17¾ years. Note 1) almost complete subluxation of the left hip, 2) flattening of femoral heads, 3) acetabular distortion on both sides, 4) narrowing of joint space on the right, and 5) decalcification. Onset of rheumatoid arthritis had been at age three with rapid progression to involvement of all joints. At time roentgenogram was taken the patient was able to walk without crutches, there was difficulty in getting up from a sitting position, and the hips had marked flexion contractures with only a little motion remaining.

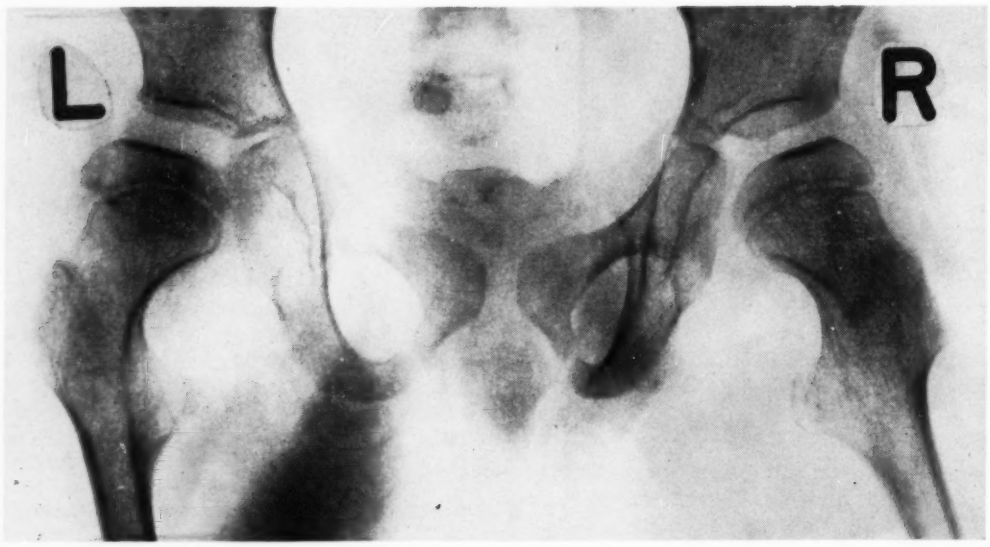


Figure 6. Roentgenogram of hips in Case 3, age 7½, seven years following onset of rheumatoid arthritis. Note 1) bilateral flattening of the femoral epiphyses similar to very early changes in coxa plana, 2) poorly seated and enlarged femoral heads, 3) flattening of the left upper acetabular margin, 4) pipe stem femoral shafts indicative of marked atrophy, and 5) adduction of right hip and abduction of left hip. At time of roentgenogram there was a bilateral 55-degree hip flexion contracture. This was reduced with traction and patient made ambulatory with crutches and braces.

ical therapy and gentle manipulation of her hips proved of no avail, and, if anything, she became worse.

When last seen as an out-patient on April 2, 1958, she was in a wheel chair and unable to walk.

Case No. 2 is a fourteen and one-half year old white girl, admitted to the Alfred I. duPont Institute in December, 1953. The past history shows that at the age of three years she complained of stiffness in her knees and became fatigued easily. She had difficulty in stooping, and in getting up from the floor, she climbed up on her legs in order to rise to an erect position. Her condition progressed and she developed a marked lordosis which was found to be due to flexion contractures of her hips. A diagnosis of progressive muscular dystrophy was made in January, 1943, on the basis of a muscle biopsy. In 1944 extension of the hips was limited to 170 degrees on the right and 150 degrees on the left. No abduction was present. Other motions were normal. In 1945 there was an increase in the limitation of extension in the hips as well as limitation of rotation. The knees and elbows now showed a limitation of motion.

On admission there was a marked contracture of the hips, knees, elbows, and wrists. The back showed limited flexion and extension with a moderat dorsal kyphosis and a lumbar lordosis. The feet were in slight equinus.

On the basis of normal creatinine and creatine studies, with absence of any clinical evidence of progressive muscular dystrophy, a diagnosis of rheumatoid arthritis was made.

Roentgenograms of the hips showed a marked subluxation of the left hip, a flattening of both femoral heads and extremely shallow acetabula, particularly on the left (Fig. 5).

Physical therapy and conservative ortho-

paedic measures improved the wrists, but the other joints remained unchanged. She left the hospital able to walk without assistance.

When last seen in the Out-patient Clinic, she was walking quite well but had difficulty in getting up from a chair.

Case No. 3 is a seven and one-half year old white girl, admitted to the Alfred I. duPont Institute in July, 1947. The past history shows that at the age of nine months, when it was found that she was unable to straighten her knees, elbows or hands, a diagnosis of arthrogryposis was made; later the diagnosis was changed to rheumatoid arthritis. From this time to her admission, there was a gradual progression of her deformities with marked flexion contractures of her knees and hips. Roentgenograms showed flattening of the epiphyses of both hips resembling an early coxa plana (Fig. 6).

Treatment consisted of skeletal traction to the lower extremities which decreased the knee and hip contractures. The deformities of the wrists and elbows were improved by conservative means. With long leg braces she was made ambulatory and was walking quite well when discharged nine months after admission.

Case No. 4 is a thirteen year old white girl, admitted to the Alfred I. duPont Institute in December, 1944. The past history shows that she was in good health until the age of two and one-half years, at which time she began to have pain and swelling in her right knee, then the left knee, followed by involvement of wrists, fingers, feet, back and jaws. Over an eight-year period she was a patient in three different hospitals, in which she had general medical treatment, physical therapy and femoral osteotomies to straighten deformities.

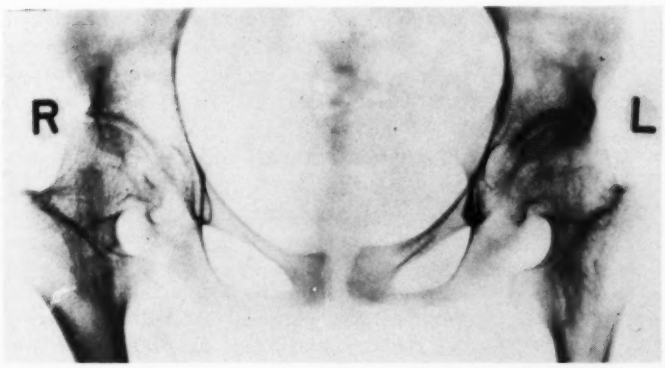


Figure 7. Roentgenogram of hips in Case 4, age 15, twelve and one-half years after onset of rheumatoid arthritis. Note 1) narrowing of joint spaces, 2) deformities of femoral heads with shallow acetabula, and 3) generalized decalcification. In spite of there being only a slight motion in hips with moderate flexion contractures, the patient was able to walk surprisingly well.

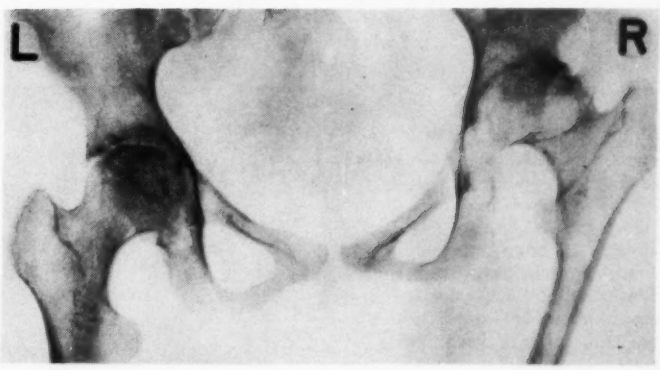


Figure 8. Case 5, age 13 years, approximately ten years after the onset of rheumatoid arthritis. Note 1) extremely narrowed joint spaces, 2) a marked adduction deformity on the right, 3) the distortion of the right femoral head, 4) abnormalities in both acetabula, 5) pipe stem femoral shafts indicating extreme bone atrophy and 6) decalcification. Patient was able to walk with crutches in spite of hip contractures and deformities.

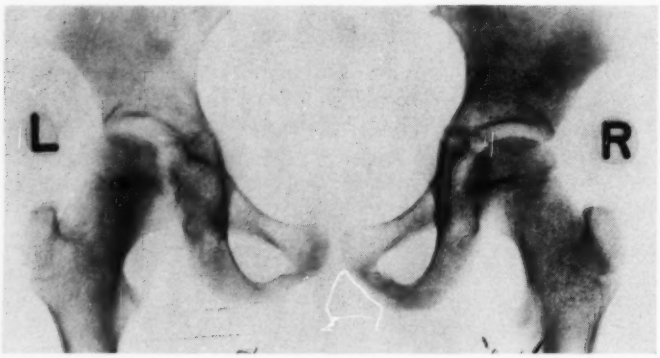


Figure 9. Roentgenogram of hips in Case 6, age 9 years, five years after onset of rheumatoid arthritis. Note large femoral head (coxa magnum) on the left which is not well seated in the acetabulum. At time of roentgenogram there was minimal disability in the hips.

On admission the patient was walking on crutches with assistance. She had a flexion-adduction contracture of the right hip, a bilateral genu valgum with a stiff left knee, a bilateral pes cavus and claw toes, an equinus deformity of the right foot, a moderate kypho-scoliosis, stiff shoulders, a bilateral wrist flexion deformity and finger contractures. She could feed herself with her right hand but not with her left. There was retraction of the mandible with a marked overbite and restriction of motion in both temporo-mandibular joints. Roentgenograms of the hips two years after admission showed a narrowing of the joint spaces with deformed and flattened femoral heads (Fig. 7).

During her two and one-half year stay in the Institute, she had repeated wedged plaster casts to correct deformities of both upper and lower evtremities, extensive physical therapy, an arthrodesis of the left wrist to give an improved functional position for the fingers, a left supracondylar osteotomy to correct a valgus deformity, and plaster cast treatment to control the progression of the kypho-scoliosis followed by a corset brace. There was a progressive increase in the stiffness in the hips with only 15 degrees to 20 degrees of motion remaining when discharged. Upon discharge she was able to walk by herself without braces and crutches, and only needed help in getting in and out of a chair.

Case No. 5 is a ten-year old white girl, admitted to the Alfred I. duPont Institute in June 1942. The past history shows that at three and one-half years of age she began to have pain, swelling and limitation of motion in the interphalangeal joints of her left hand; at which time a diagnosis of rheumatoid arthritis was made. This progressed to a severe generalized joint involvement restricting her to a bed or chair by the age of seven.

On admission she was unable to walk. With general supportive treatment, physical therapy and long leg braces, she was made ambulatory and discharged in eight months. Two years later she was readmitted with a recurrence of the deformities

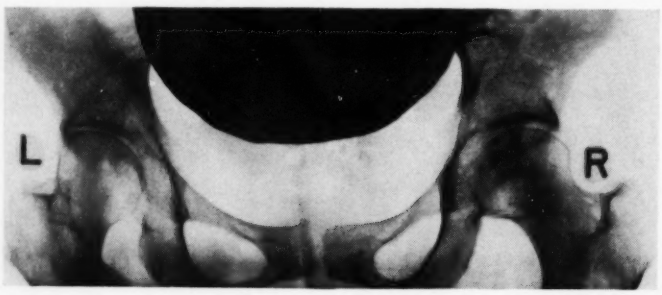


Figure 10. Roentgenogram of hips of same patient as in Figure 9, ten and one-half years later. Note moderate deformity of head of left femur with narrowed joint space. No evidence of coxa magnum. At time of roentgenogram there was a slight limitation of internal rotation in the left hip with occasional discomfort.

and again unable to walk. A triple arthrodesis was performed on the left foot to improve the weight bearing surface. With traction, gentle manipulation and braces, she was again made ambulatory. During this second admission, roentgenograms of the hips in October, 1946, showed the marked changes as seen in Figure 8.

In April, 1948, when readmitted for the third time, she was able to walk unsupported but had pain in her left leg, foot, knee and hip. The stiffness and deformities in all of her joints and spine had now increased. The hips showed 45-degree flexion contracture with the right hip being ankylosed in adduction and internal rotation and the left in moderate abduction. In May, 1948, a subcutaneous adductor tenotomy was done on the right to correct the adduction deformity. However, in spite of intensive post-operative physical therapy, there was recurrence of the deformity in six weeks after operation. When discharged, she was ambulatory with braces and crutches.

When last seen in the Out-patient Clinic in November, 1949, she was in a wheel chair and unable to walk.

Case No. 6 is a seven and one-half year old white girl, admitted to the Alfred I. duPont Institute in June, 1946. The past history shows that when she was four years of age she had an injur yto the right knee which became swollen and stiff. This was followed by pain and stiffness in the left knee, hips and fingers, and a diagnosis of rheumatoid arthritis was made.

On admission there was limitation of motion in the right knee and proximal inter phalangeal joint of the right index finger without other joint involvement. Improvement in motion in the knee was obtained with physical therapy and in the finger with a Banjo splint. While in the hospital she developed pain and stiffness in the knees and hips. She was discharged in nine months. Roentgenograms of the hips at time of discharge showed a large femoral head on the left which is not well seated in the acetabulum (Fig. 9).

In 1948 she was readmitted because of valgus deformities in both knees. These deformities were corrected by tibial osteotomies. At this time there was a complaint of discomfort in the hips; however, they were normal on examination.

Figure 11. Roentgenogram of hips in Case 7, age 8 years, two years after onset of rheumatoid arthritis. Note 1) fuzzy abnormally shaped epiphyses, 2) increased calcification on either side of epiphyseal line, 3) slight narrowing of the joint spaces, and 4) decalcification. At the time of this roentgenogram there was some limitation of motion in both hips and there had been steroid therapy for six months.

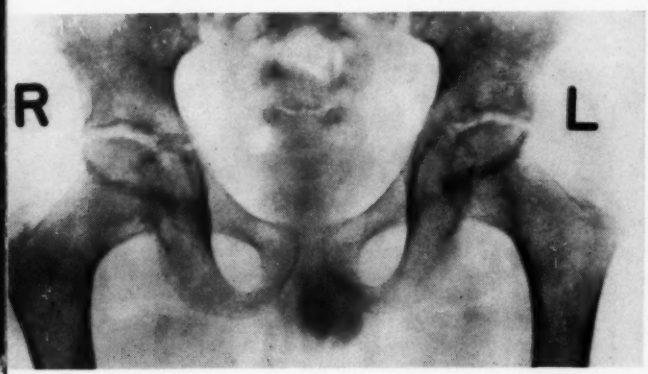
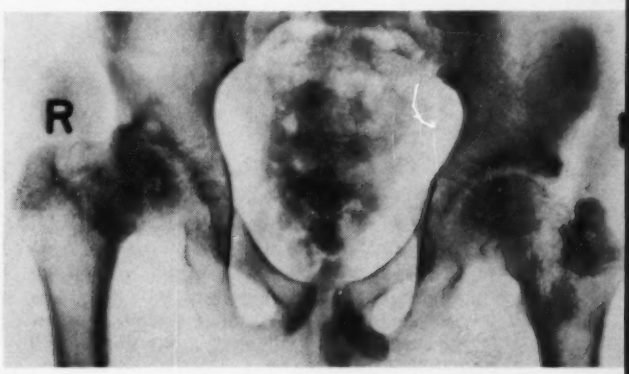


Figure 12. Roentgenogram of hips of same patient as in Figure 11, five years later at age 13. Note 1) a flattened irregular right femoral head with no epiphyseal line, a shallow acetabulum and a mild subluxation, and 2) that the head and neck of the left femur suggests an old healed coxa plana. At the time of this roentgenogram weight bearing caused definite pain in the left hip.



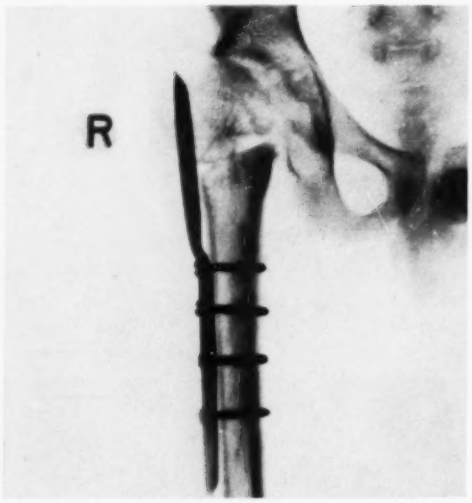


Figure 13. Roentgenogram of the right hip of the same patient as in Figures 11 and 12 immediately following a McMurray displacement osteotomy, held with a blade plate. This roentgenogram was taken seven weeks after Fig. 12.

She was readmitted for the third time in 1949 for physical therapy to her right knee. At this time there was a slight limitation of abduction in the left hip.

In March, 1951, she was readmitted for the fourth time, because of severe progression of the disease which now involved nearly all joints, particularly the right wrist and knee. A left supracondylar osteotomy was done to correct a genu valgum deformity, which was followed by an arthrotomy of the left knee to remove a large hyaline cartilage sequestration. Also, an epiphyseal arrest was done on the left lower femoral epiphysis because of an overgrowth of this femur. ACTH was given with "moderate but gratifying" relief of symptoms. The hips were moderately stiff.

During the fifth admission in September, 1953, the left wrist was fused in a position of function. No activity of the rheumatoid arthritis was noticed Her hips were now freely movable in all directions.

At the time of her last visit to the Outpatient Clinic in July, 1958, there was occasional discomfort in her left hip with slight limitation of internal rotation. Roentgenograms showed a deformed head of the left femur and a narrow joint space (Fig. 10).

Case No. 7 is a six and one-half year old

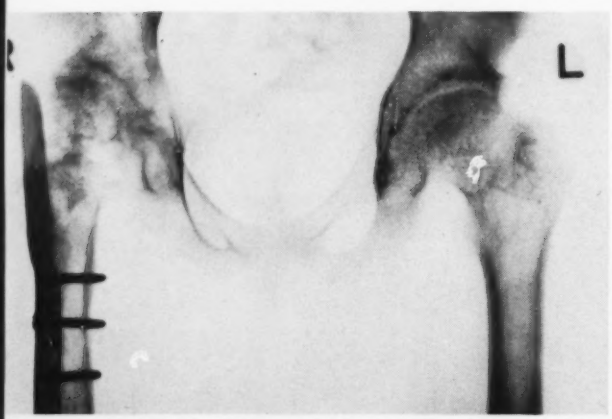


Figure 14. Same patient, one year after McMurray osteotomy. Note 1) the well-healed osteotomy, 2) the almost complete disappearance of the joint line on the right, 3) the two breaks of bone on the medial side of the osteotomy side, 4) the large flattened and distorted head of the left femur suggesting an old healed coxa plana.

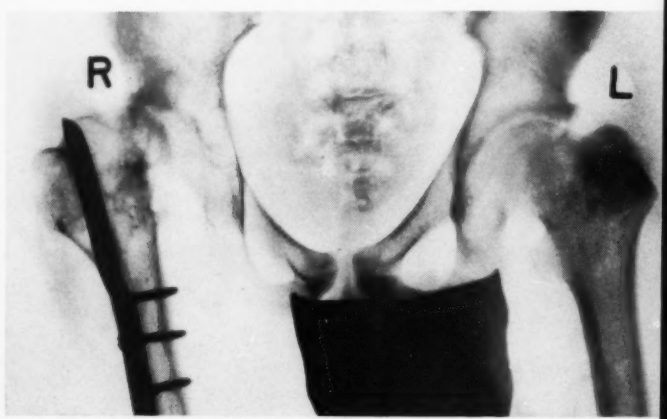


Figure 14a. Roentgenogram of the same patient as in Figure 14, at age 15 years, two years after McMurray osteotomy. Note 1) in comparing this roentgenogram with Figure 14 there is a very definite increase in the subluxation of the right hip with an adduction deformity, and 2) the right acetabulum is extremely shallow as compared with that on the left.

white boy, admitted to the Alfred I. duPont Institute in January, 1950. The past history shows that six months prior to this time he developed a painful and swollen right knee which was followed by a similar involvement of the left knee. During the next three to four months, the ankles, elbows, wrists, hands, and feet became involved, while he ran a febrile course and was confined to bed. A diagnosis of rheumatoid arthritis was made.

After admission he continued to run a septic course for several months with severe generalized joint involvement and a soft systolic murmur. On admission there were 20-degree flexion contractures in the hips with mild limitation of internal rotation and abduction. The knees had moderate contractures. The hip and knee contractures were reduced with skin traction, this was followed by splints and physical therapy. He was discharged six months after admission with only a mild limitation of hip motion.

In October, 1950, he was readmitted with an exacerbation of all joint symptoms. With ACTH, his symptoms decreased and his walking improved. Roentgenograms of the hips in March, 1951, showed fuzzy epiphyses and decalcification (Fig. 11). In June, 1951, there was practically no restriction of hip motion. A fracture of the left femur occurring in 1951 healed uneventfully.

In 1955 a limp on the right developed because of hip pain on weight bearing. Six months later there was an adduction deformity of the right hip with marked limitation of all motion and a three-fourths inch shortening of the right lower extremity. Roentgenograms in February, 1956, showed a flattened, mushroom shaped right femoral head with a shallow acetabulum and beginning subluxation (Fig. 12). A McMurray subtrochanteric displacement osteotomy was performed in March, 1956 (Fig. 13). Upon weight bearing three months later, there was a complete absence

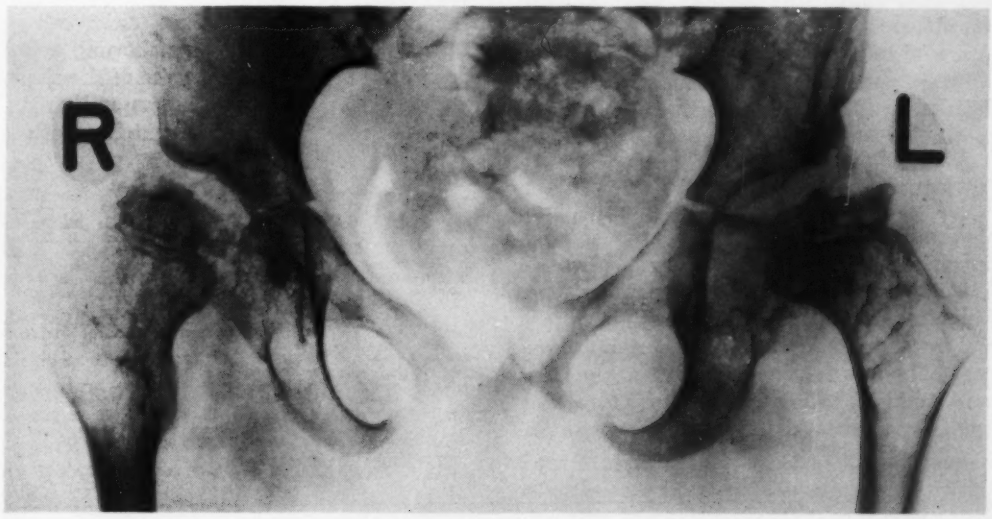


Figure 15. Roentgenogram of the hips in Case 8, age 5 years, two and one-half years after onset of rheumatoid arthritis. Note 1) large head and neck of both femora, 2) irregularity of both epiphyses with an eroded area on the left, 3) shallow acetabula with imperfect seating of the femoral heads suggesting a mild subluxation, 4) pipe stem femoral shafts indicating extreme bone atrophy, and 5) marked decalcification. Fourteen months prior to this roentgenogram, the left hip had a pathological dislocation requiring an open reduction. There was a marked limitation of motion in both hips but the patient could ambulate with braces and crutches.

of pain. Ten months after the operation, the roentgenogram showed that the osteotomy had completely healed and the relationship of the head of the femur to the acetabulum was definitely better than prior to operation (Fig. 14). However, the roentgenogram taken one year later, and approximately two years following the operation (March, 1958), showed further subluxation of the head of the femur with a definite adduction deformity (Fig. 14a). When last seen in December, 1958, he was completely pain free and walking quite well with only a slight limp.

Case No. 8 is a five year old Negro girl, admitted to the Alfred I. duPont Institute in April, 1955. The past history shows that at the age of two and one-half years in March, 1952, she had an otitis media which was followed in four months by joint swellings. In March, 1954, the patient was admitted to a local hospital in acute distress, with multiple joint involvement and flexion deformities of the knees, shoulders, and elbows. The treatment consisted of Cortone, supportive therapy and traction for flflexion deformities of hips and knees, followed by plaster cast wedgings. In July, 1954, a pathological dislocation of the left hip occurred requiring an open reduction.

On admission she showed marked involvement of all joints of the upper extremities with pain, limitation of motion and deformities. The lower extremities showed involvement of the hips and knees with complete absence of motion. There was a genu valgum deformity on the left with an internal rotation deformity of the right lower leg. There was some motion in the feet and ankles. All attempts to move the joints were painful. The lower extremities were splinted and the acute condition gradually subsided. Physical therapy and gentle manipulation of the joints were begun after a month. A slight increase of motion in a few joints was obtained. Steroid therapy was of no benefit. Roentgenograms of the hips at this time showed irregularity of both upper femoral epiphyses, especially on the left, shallow acetabula and imperfect seating of the femoral heads (Fig. 15).

Two months after admission a pathological fracture occurred in the left lower femur; then one week later fractures occurred in the right upper tibia and fibula; and two and one-half months later in both tibiae. In November, 1955, Testosterone and Stilbesterol were started in an effort to improve the general condition and possibly aid in recalcification of her severely demineralized bones. In January, 1956, the patient was able to ambulate a little with braces and crutches with a very slow gait. In early April, 1956, a reduction in the hormonal therapy was begun. There had been two episodes of slight menstruation. Upon discharge, thirteen months after admission, the patient was ambulating fairly well in braces with knees and hips showing a few degrees of motion, and in spite of the slight flexion deformity of the fingers and wrists, she was able to hold her crutches with a good grip.

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TRANS-ATLANTIC CLINICO — PATHOLOGICAL CONFERENCE

Medical Society of Delaware and the Royal Society of Medicine.

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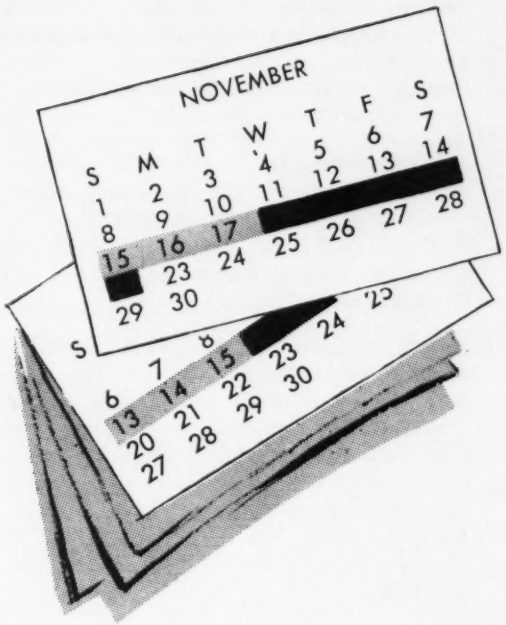

● The second part of a discussion on this frequently troublesome condition is concluded in this issue. Part I appeared in the November Journal.

DYSMENORRHEA AND PREMENSTRUAL TENSION*

O. N. Stern, M.D.**
H. Keith Fischer, M.D.
Laurence L. Fitchett, M.D.
Abraham S. Rakoff, M.D.

We can see from this discussion that Dr. Fischer has given us, that the psychiatric plays a big part in the question of dysmenorrhea. However, for years the medical profession, or should we say within recent years, has been imbued with the idea that a misplacement of hormonal balance is the real causative factor in the production of dysmenorrhea. It is interesting to note that the average girl who begins to menstruate does not have dysmenorrhea. She only develops that dysmenorrhea when she begins to ovulate. So the girl who has dysmenorrhea, if she has no psychiatric factor behind it usually can consider herself as being in an ovulatory phase of that particular menstrual cycle. The question of hormones is quite vast. There is quite a disagreement among the various gynecologists as to which is the proper factor. In fact, in addition to hormones, certain other facets of therapeutics have been investigated. We know that McKnight and Butler have gone very thoroughly into the question of vitamin E, or alpha tocophorol and they have proven that they have a certain amount of relief with this drug, believing that the vitamin E causes an increased vasodilatation of the terminal arterioles and therefore decreases the spasm of menstruation. We also have the work of Hezzeltine who went into the question of ACTH. That work was quite inconclusive because of the fact that out of twenty-nine patients that he reviewed, sixteen of them only had primary dysmenorrhea and the follow-up as to results of the treatment was not thorough.

I would like to introduce now Dr. Abraham Rakoff, Professor of Clinical Gynecology, and head of the Endocrinological Division of Jefferson Medical College, to discuss this facet of the symptom complex of dysmenorrhea. Dr. Rakoff.

Dr. Abraham Rakoff: Dr. Stern, member panelists; members of the Delaware State Medical Society:

*Panel discussion presented at the annual meeting of the Medical Society of Delaware, Wilmington, October, 1957.

**Moderator of Panel.

Dr. Stern in his opening remarks pointed out very succinctly that dysemnorrhea is a symptom, and as a symptom can be induced. by many different factors. It is a symptom which to my mind is the result of nothing more or less than uterine colic, and like colic from many structures can be influenced in many ways.

Dr. Fitchett pointed out that there are many patients with dysmenorrhea of a mild degree who respond to ordinary analgesics and anti-spasmodics.

Dr. Fischer pointed out that there is also an important psychosomatic element in uterine colic.

The Endocrine Factor

Now, so far as the endocrine factor in dysmenorrhea is concerned, I think the endocrinologist is interested in dysmenorrhea from a number of different standpoints. First of all, he is interested in dysmenorrhea because it is a very aggravating problem to him because most patients with dysmenorrhea are endocrinologically normal, as I will soon point out. But yet he can influence dysmenorrhea by making that patient endocrinologically abnormal, and again he can also select those patients who might have some psychogenic or organic cause for their dysmenorrhea by the way they do or do not respond to hormones. And finally, he is interested in dysmenorrhea because he can also influence this symptom with various hormones.

Dr. Stern pointed out that the great majority of patients with ordinary cramps do not develop dysmenorrhea when they first begin to menstruate. Their first year or two of menstrual life may be perfectly normal and it is not until the ovary has matured and has learned to ovulate so to speak and the endocrine cycle is complete that that dysmenorrhea develops.

Now, the uterus is under the control of many of these hormones that are produced by the ovary. During a normal menstrual cycle we find that estrogen rises progressively to reach its peak at the mid-cycle.

Now, we know that estrogen increases uterine tonus. Is estrogen therefore a factor by increasing uterine tonus and increasing uterine contractions in producing dysmenorrhea?

Contrarywise, Dr. Stern pointed out that estrogenes induce vasodilatation, which would tend to counteract dysmenorrhea. And as I will point out a little later, we also know that estrogenes can be used to treat dysmenorrhea.

Now, we know that the patient who menstruates perfectly normally produces progesterone, and we are taught that progesterone is the normal uterine sedative and that progesterone inhibits uterine contractions, and therefore progesterone ought to be good for dysmenorrhea. Yet on the other hand we know that the great majority of girls who have dysmenorrhea produce progesterone.

On the other hand, as Dr. Stern already pointed out, progesterone produces vasoconstriction. Does this ischemia favor dysmenorrhea? The point I am trying to make is that for almost every hormone you can build a case why it should aggravate dysmenorrhea or why it should help dysmenorrhea. But if you had to pick from a room full of women, one hundred women, let us say, who are endocrinologically normal, I would select those hundred women who have ordinary cramps, because if we study those patients carefully from an endocrine standpoint we know that they are the women who in the highest majority of cases are going to be fertile, that you are going to find normal secretory endometria and who by all studies that we do endocrinologically, are going to turn out to be normal. There will be exceptions, about 15 per cent. But 85 per cent of them, which is a good per cent, are going to be perfectly normal.

Dysmenorrhea a Symptom Complex

That is the first point I would like to make, that the patient with ordinary dysmenorrhea is usually quite normal and that

dysmenorrhea is a symptom complex of the endocrinologically normal woman.

One might say then that the changes that these normal hormones produce on the endometrium in preparation for menstruation may be creating some substance within the uterus which is an irritant, and that when menstruation occurs it is truly, as has been said, the bloody tears of a disappointed uterus in which conception did not occur and that therefore there is pychogenic induction of bleeding or pain on the basis of some biochemical change. Well, we know that progesterone does cause the deposition or the formation in the endometrium of acetylcholine and that acetylcholine induces changes in the blood vessels that eventually cause bleeding. Does acetylcholine cause dysmenorrhea or uterine contraction? It has been shown that acetylcholine does not aggravate dysmenorrhea, and if anything, acetylcholine is a vasodilator which alleviates dysmenorrhea.

If estrogen is given to a rabbit the uterus goes into rather marked uterine contractions. If progesterone is then given, the uterine contractions become inhibited and gradually fade out and disappear altogether, which would indicate that progesterone, as I said before, ought to be helpful in the treatment of dysmenorrhea, and yet we know from practice that only occasional patients are helped by progesterone and that as a matter of fact it is the patient who produces normal amounts of progesterone who is more susceptible to dysmenorrhea.

The only type of dysmenorrhea that I know of which is due to a true endocrinopathy is the so-called membranous type of dysmenorrhea, the patient who passes a cast, a decidual cast with her pain. If you study patients of this type we do find they produce excessive amounts of progesterone which causes the formation of a decidual cast, with mechanical irritation.

And if such endometria are sectioned we see excessive decidual reaction.

The Non-ovulatory Cycle

It was discovered that one of the almost sure ways of alleviating dysmenorrhea is to create artificially a non-ovulatory cycle. We can do this in many different ways. One of the easiest and simplest ways it to give estrogen early in the cycle. Estrogen will inhibit the pituitary (f.s.h.) and therefore the ovary will not go on and ovulate.

For this purpose one can use, for instance, Premarin, 2.5 milligrams, twice a day, beginning as soon as the menstrual period is over, and giving it until four or five days before the period is due. When one does this, then the subsequent bleeding is simply an estrogen withdrawal bleeding, and almost always in true essential dysmenorrhea this is painless bleeding and the patient comes back extremely gratified. What is this wonderful medicine which for the first time in her menstrual life has produced a symptomless period?

This gratification, of course, does not last too long, because if you then give this medication the next month, the pituitary escapes, the pituitary finds it has to go to the next higher level, which it does. And in spite of estrogen, the gonadotropins break through, the patient ovulates, as you can prove by basal temperature charts, if she is keeping one, and she has a painful period, and she is extremely disappointed.

This brings up the important point that if you are going to use estrogens for the treatment of dysmenorrhea, you cannot use it continuously. And the best plan to do in such instances of severe dysmenorrhea where you plan to use this type of therapy is to give the estrogen every other month. In this way the patient can be assured of six painless periods out of the year. And this is advisable also because it is not wise to inhibit the pituitary and ovary continuously. By so doing we may produce atrophy of the ovary and later trouble. But if we give it every other month the patient ovulates one month and has a painless period the other month, which leaves us then with six painful periods to cope with by other methods.

Now, that is one way of inhibiting ovulation.

Another way of doing it is to give androgens. One can give androgens again beginning about the sixth or seventh day after the onset of menstruation in the form of methyl testosterone, 10 milligram tablet, three times a day, for about six days. One does not have to give it throughout the cycle. If you give it for about six days, then the subsequent period is often painless. Sometimes ovulation is inhibited by basal temperature chart, and sometimes it is not. But even when it is not, very frequently the period that comes after androgen therapy is painless.

Still another way of inhibiting ovulation for this purpose is with the use of progesterone. Now, progesterone given in the preovulatory phase will also inhibit ovulation. Some of the new progesterone compounds are especially effective in inhibiting the pituitary. I am speaking now of Norluton, a Parke Davis product, and Enovid, made by Searle, which are the two new potent oral progesterone compounds. One can give ten milligrams a day, beginning as soon as menstruation is over and give it for twenty-one days. Ovulation is inhibited. The patient has bleeding from a progesteronic endometrium, which is often painless but it is not as universally painless as you get with estrogens. But for the patient in whom it works it has this great advantage. You can give it month in and month out. The pituitary does not seem to escape in those instances.

Other Hormonal Therapies

Now, in addition to these methods of inhibiting ovulation, there are several other types of hormonal therapies that can be used to overcome uterine colic. Androgen given late in the cycle seems to have some effect in some patients. For this purpose one has to give 25 to 50 milligrams of testosterone propinate by injection about three days before the expected period. In some patients this will work; in other it will not.

Still another hormone which is sometimes valuable is Relaxin. As you know, Relaxin is a water-soluble steroid hormone of the ovary, in its pure form extremely expensive, but some impure preparations are available for oral use such as Nutrexin. Nutrexin comes in tablets of 1,000 units and two or three tablets given every three hours for four doses just before the onset of menstruation will also sometimes inhibit uterine contractions.

I said before that hormones are also valuable in the selection of patients so far as their diagnosis is concerned. We find that — and many others have found — that if you give patients estrogen, in adequate dosage, such as Premarin two and a half milligrams twice a day, and then the subsequent bleeding is painful, instead of painless, despite the fact that basal temperature charts show that ovulation was inhibited, then to my mind that usually means that the patient does not have the ordinary type of primary or essential dysmenorrhea; it means either secondary dysmenorrhea due to an organic factor you have overlooked, which you should now go back and restudy, or if you can't find that, it means that the dysmenorrhea is on a psychogenic basis, and the very fact that the patient bleeds is enough to induce the psychosomatic syndrome which Dr. Fischer has described.

It is helpful then in making a selection of patients and helping you to decide which one should and should not be treated certain ways. It is also helpful in selecting which patients, if any, should have surgery, and no doubt Dr. Stern may speak later about the use of surgery in intractible cases of dysmenorrhea. Certainly the patient who does not get relief from estrogen is not a good candidate for surgical therapy because she has a very good possibility of having a psychogenic basis and will simply develop a new type of symptom complex surgery will not be of any help in her case.

There has been another new facet, I think, which has been of great interest to the endocrinologist in this interesting

symptom complex, and is the role of Oxytocin. All of us know that Oxytocin is a uterine stimulant. It stimulates uterine contractions, and we would therefore expect Oxytocin if anything to aggravate dysmenorrhea. Yet some very good studies recently have shown that Oxytocin given by injection to the dysmenorrhea patient will relieve dysmenorrhea for several hours; whereas Pitressin will markedly accentuate dysmenorrhea. This brings out the vascular factor in dysmenorrhea. Pitressin produces of course vasoconstriction. Oxytocin, even though it induces uterine contractions, induces vasodilation of the uterine blood vessels, which indicates then possibly, that in dysmenorrhea we have an organ which is ischemic, and that when this ischemic organ goes into contraction we have pain due to contraction of an ischemic structure, and that for that reason, therefore, Oxytocin would be a medication which would relieve dysmenorrhea, Pitressin one which would aggravate it, and therefore there is a big hunt on now for substances which have an anti-pitressin-like activity as a logical medication in the treatment of dysmenorrhea.

So you see that there are a number of very interesting facets to the endocrinology of dysmenorrhea.

CHAIRMAN STERN: Thank you, Dr. Rakoff, for that very interesting discussion.

Before we open the panel up for discussion from the floor, I think it might be wise to review briefly some of the surgical aspects of the treatment of dysmenorrhea.

The Stem Pessary

Years ago the stem pessary was quite a factor in the treatment of this condition. Then because of the fact that it caused a severe endocervicitis, it was thrown to the side. But recently it has returned in the treatment of dysmenorrhea because Reynolds has shown that the stem pessary, which is inserted and left in place for a matter of several months, causes mitosis and definite enlargement of the muscular cells of the uterus, even more quickly than does estrogen itself.

Therefore frequently the stem pessary in the hypoplastic uterus can cause enlargement and in that way produce regular groups of contractions rather than individual isolated contractions which they believe occur in the hypoplastic uterus. This frequently can be of benefit. We know definitely that cervical dilation in 81% of all cases does relieve primary dysmenorrhea.

The factor here, of course, relates to the same principle that child bearing will relieve 81 to 85 per cent of all primary dysmenorrhea. The factor here is the disruption of the nervous impulses rather than opening up the canal. We know that obstruction per se is not a factor today. It is rather a factor of destroying the end plates in the cervix and the surrounding tissue by forceful dilatation of the cervix.

Lastly, we must consider and correct retroflexion of the uterus before considering more formidable surgical procedures such as presacral neurectomy. But now we arrive at the factor of when to do a presacral neurectomy.

This question has many facets. There are many schools that agree that it should be done in only certain cases. There are other schools that say it should be done as a routine in every case in which the patient has dysmenorrhea and the doctor has to go in and do some pelvic surgery. How to choose the patients that you operate on, Dr. Rakoff has brought out. If they are relieved with estrogen, most of these patients will respond to presacral neurectomy.

Anderson, in Toronto, uses a different test. He gives his patient sodium amytal in the office intravenously, waits three minutes. If the patient says that she is relieved of her pain, he considers it a pychosomatic. If the patient is not relieved he believes that she is a candidate. That I have had no experience with. Possibly some of the members on the floor have.

In doing a presacral neurectomy I would like to go into two factors. Dr. Phaneuff at the Tri-City meeting in Boston in 1950,

in reviewing eighty-six cases in which he did presacral neurectomy, brought out the factor that unless a wide presacral neurectomy is done — by that I mean that the vessels are stripped, the ureter, etc. — there is no definite guarantee of results. He also brought out the fact that in doing this, one should strip down only so far and not below the promontory of the sacrum, because by doing such, possibly danger or damage to the bladder function and bowel function can occur.

With these few words I would like now to turn over the meeting for discussion from the floor. Are there any questions?

DR. LEVINSON: Some of the older books make mention of exercises in the help of dysmenorrhea. I would like to know if you men feel that this is of any help.

Also the uterine suspension which is frowned upon largely today, do you ever feel there is a place for that today? And also I would be interested to know in the practice such as Dr. Rakoff's, how often he feels that he finds candidates for presacral neurectomy or ovarian neurectomy and so forth.

Exercises to Alleviate the Condition

DR. RAKOFF: First of all, so far as exercises are concerned, I think it has been a common observation among girls who are athletes and ballet dances and so forth, that if they exercise vigorously the day before their menstrual period is due, they are much less likely to get dysmenorrhea, and some of them have noticed this so strikingly that they do that as a routine. And that has been the basis for the so-called billig exercises. Dr. Lee Gollip in Philadelphia has been running a clinic among the high school girls, and he has instituted these billig exercises, which are exercises for tilting the pelvis forward, backward and sideward, during the pre-menstrual phase, and he has found that an appreciable number of them, not all, but an appreciable number seem to be benefited.

He has been very interested in why this works. He believes that in some of these patients, at least, that the ileohypogastric nerve comes out in between the muscle instead of on top of the rectus muscles, and that in the pre-menstrual phase there is edema which presses on these muscles, and that that may be a factor. Just how exercise helps this I am not quite certain.

Now, so far as the number of cases that I see that are candidaes for surgery, I think this varies somewhat in the community you are in and how you are oriented. In Boston they seem to find many patients that should have presacral neurectomy, and it is a very popular operation in Boston. In Philadelphia it seems to be a very uncommon operation.

I think a lot depends on just how willing you are and how conscientious you are to find some conservative method of treatment first, and whether you are willing to exhaust all the possibilities. I think that if you go through the list of things with the patient, that almost always you can find some combination of therapy which will be satisfactory to tide that youngster over for a while, and then you hurry up and encourage her to get married and have a baby, which is the best cure of all.

But I personally have only seen two or three patients in the many thousands in the last ten years that required presacral neurectomy as the only out for this condition.

Are there any other questions?

DR. CHAVIN: Isn't it true that if you give a hypodermic of one cc. of Demerol at the height of dysmenorrhea, which is about the first day, the dysmenorrhea does not return for the rest of the period, for five or six days?

DR. RAKOFF: To most patients that have dysmenorrhea, it is only the first day usually which is intolerable, and it is true that Demerol will relieve or carry patients through that first day. However, I think it is not a good thing to get the patient into the habit of calling the doctor each

mnth for a shot of Demerol, because many of us have seen patients who have gotten pretty fond of this type of therapy. I think it is something that might be all right once for an emergency, or for special circumstances, but certainly not for routine therapy.

CHAIRMAN STERN: Thank you, Dr. Rakoff.

Are there any other questions?

DR. SLOVIN: I would like to ask Dr. Fischer what is the psychiatric approach to the treatment of a patient who is referred to the psychiatrist for dysmenorrhea. Do they go into analysis or just exactly what is done and what is the percentage of good results?

DR. FISCHER: I guess the vast majority of patients that are referred to psychiatrists with dysmenorrhea are really being sent for pretty deep and complicated personality problems of which dysmenorrhea is the present symptom. If the symptom is seen first and early by a general practitioner who is interested in talking about emotional problems, some very gratifying and remarkable things can happen which will benefit a number of patients.

Actually when you ask the question of statistics, I can't give you these. My own experience with dysmenorrhea, patients with dysmenorrhea, who come either primarily for that or have dysmenorrhea along with other conditions, have certainly indicated that the results of effective psychiatric treatment apparently give much more gratifying and prolonged relief than many of the treatments I have heard here discussed. I suppose it is both a good thing and a bad thing that so many treatments influence this symptom. But again if we are going to be physicians on a sound basis, we have got to do more than treat symptoms. We have got to treat causes. And until the psysiologist can get down a little more to the question of causes and sources, then I suppose we will treat it on the basis of what our main interest is in, are we surgeons, are we internists, are we psychiatrists or endocrinologists?

Now, the treatment these days, psychoanalyses is reserved for very special cases, you don't psychoanalyze the average patient. It is too formidable in time, cost and effort. On the other hand, we are trying to develop a goal directed psychotherapy that does assist in short range problems. This won't take disturbed, mixed-up persons and change them into brand new people by any means; but we are trying to learn a psychotherapy that is applicable in maybe five or ten visits and make significant changes. This is difficult, but I would think we are gaining on it.

I would say, first, the local physician who sees the patient should spend a little time seeing whether there is some emotional problem directly related to this, and frequently he would be quite surprised and gratified as to what can happen with a very little bit of time aimed in this area.

CHAIRMAN STERN: Are there any other questions?

DR. REPMAN: Dr. Rakoff recommended the use of estrogen for treatment of dysmenorrhea every other month. I recall Dr. Emil Novak frowned upon the use of estrogen, especially in menopausal women on account of the enlargement of the uterus, and so forth. Do we have partially the same thing in the treatment of your therapy?

DR. RAKOFF: First of all, we are dealing with young women here so we don't run into exactly the same contraindications or fears of prolonged estrogen therapy as you would in the woman who is approaching menopause, when she is getting into the so-called cancer age. I know of no young woman in whom cancer was induced by estrogen therapy. On the other hand, I do think that continued estrogen therapy has certain drawbacks, mainly the inhibition of the pituitary and the ovary. When it is given every other month I have not found it to be harmful. The pituitary and ovary have always bounced back, and the in-between months have been ovulatory.

So I think when used every other month it is, shall we say, less undesirable. I admit that this is not the treatment of choice, but I don't know of any treatment of choice for dysmenorrhea.

For the intractible case it is one way out and I think that used every other month, you are not likely to get into difficulties. Once in a while you will meet a young dysmenorrheic girl to whom you give estrogen in this fashion, who has hypoplasia of the uterus, in whom your estrogen therapy produces a better developed uterus, who may then go on for six or eight months and be free of her dysmenorrhea.

The Psychogenic Factor

While I am here, I would like to comment a little bit on the psychogenic factor, Dr. Fischer, in this sense. I think all of us who deal with functional disturbances in gynecology have been extremely impressed with the sensitivity of the pituitary ovarian mechanism to psychogenic factors, and all the different kind of syndromes that psychogenic factors can produce in women, and I would like to point out that sometimes a patient who has severe dysmenorrhea who is otherwise, as far as we ordinary doctors can tell, psychogenically all right, and becomes emotionally disturbed, may develop a pituitary ovarian disturbance which cures her dysmenorrhea; that is, we know that emotional factors can produce a non-ovulation. And with the anovulatory cycle the dysmenorrhea may go. I am not recommending this as a type of therapy to produce an emotional disturb- is one of the things that happens.

Sometimes when we see patients who give ance for the cure of dysmenorrhea. But it us a history of infertility and they tell us that previously they had dysmenorrhea and then more recently, since they are married, for instance, their dysmenorrhea has disappeared, we are very suspicious that they have developd an anovulatory infertility as a result of psychogenic problems.

CHAIRMAN STERN: Thank you, Dr. Rakoff.

Are there any other questions?

DR. CANNON: I have two questions, one rather frivolous. What is the derivation, Dr. Fischer, of "off the roof" as a vernacular? In urology we have a lot of vernacular expressions that are quite interesting. I was wondering if you could enlighten us on that.

Secondly, what is the relation of dysmenorrhea and alcoholism in women, because I have known from a few experiences, patients who resorted to alcohol as a method of relief; whether that has psychogenic overtones or whether it is an effective measure of therapy.

DR. FISCHER: I am afraid you are going to be disappointed in the answers to both of your questions. The first is, we spend a good deal of time trying to understand the symbolic meaning of little phrases that people use, and of course most of the phrases that are used to designate menstruation are fairly obvious. The one about the "off the roof" still has me puzzled, and I have a large group of women that are hunting to give me the answer to this. I don't know where it came from.

Incidentally, those of you that get the Encyclopedia Britannica know you get a group of fifty stamps that you could send in for research studies of cultural and social things. I use them quite frequently. There are many things in my business I have to turn to, and maybe I will ask whether Encyclopedia Britannica can help me with that one. I don't know where it started, but it has developed and it must have some basic symbolic meaning. It has caught hold, and these things that are generally popular do have some symbolic foundation, but I don't know what it is.

DR. CANNON: "The curse," I know that is used.

DR. FISCHER: Yes, "the curse."

The second question about the relationship of alcoholism to dysmenorrhea, I don't know; I have never studied the two directly, and I suppose those who have

studied alcohol primarily could tell about it. I think women frequently have their own methods of treating their own dysmenorrheas, and whether it is the hot water bottles or special foods or so forth, they have their own little tricks, just as well as we have these scientific tricks for trying to handle it. But I can't give you a definite answer.

DR. RAKOFF: Gin is a very common thing.

Marriage and Pregnancy

DR. HYNES: I am not sure to which member of the panel to address this. It might be the psychiatrist or the endocrinologist or even to the surgeon who prescribes exercises. What is the reason that many patients with dysmenorrhea are relieved by marriage, not including pregnancy, just by marriage?

DR. FISCHER: I think it is psychological, and I think the difference is a difference in emotional investments, that the girl who has her menstrual period as a central emotional investment is preoccupied with the thing. When she has sexuality, babies and other things, her emotion gets changed around a little bit.

I included as a part of the paper here some verbatim words by one of these women who had severe dysmenorrhea, then trouble, and habitual abortions and so forth, and I think the answer probably has to do with difference of emotional investments. I might also say that if Dr. Rakoff got up in one of my classes and said he advocates pregnancy or marriage as a therapeutic thing, I would say, "That is declaring war." While this is another social maneuver that may influence a symptom, it raises far more problems than it solves. And it is this kind of stuff that is going to give a psychiatrist more patients than he can handle.

DR. FRELICK: Dr. Fitchett, I believe, is the only one who discussed premenstrual tension as part of dysmenorrhea. I was wondering whether these two are related and if so what the correlation is.

Furthermore, I would be interested in the psychiatric treatment of premenstrual tension, whether psychotherapy is of value or whether the hormones are — diuretics may be of more value. I think the disturbed woman who can be helped by medicine is a very dramatic finding, and is the help to be given to these people only psychotherapeutic or are we going to do other things?

DR. RAKOFF: Well, in young women there is an association between premenstrual tension and dysmenorrhea, because, as I pointed out, the woman with dysmenorrhea is secreting more steroid hormones. She is making adequate amounts of both estrogen and progesterone, both of which tend to cause fluid retention, and both of which would favor the syndrome of premenstrual tension as a result of fluid, salt and water retention.

So I think that there is this relationship between the two. And there are some investigators who feel that it is the salt and water retention which may produce a pelvic neuritis, so to speak. I have always been fascinated by the fact that some of the surgeons who remove these bits of nerve tissue at presacral neurectomy claim that there is a perineural neuritis in the nerves that they remove.

CHAIRMAN STERN: I might add that we have talked about presacral neurectomy. There are certain types of menstrual pains that presacral neurectomy does not relieve. Only by cutting the plexus in the infundibulopelvic ligament is the so-called ovarian dysmenorrhea relieved.

Are there any other questions?

Premenstrual Tension

DR. DEWEES: In line with what Dr. Frelick has said, in my own experience a lot of these girls who have premenstrual tension do not have very bad menstrual cramps, but they feel terrible and they are hard to get along with, and nobody can do anything right or fast enough for them in the three or four or five days before their period. If you put them on the scales every

morning a lot of them will be shown to gain two or three pounds during this period. But in my experience a lot of those girls don't have very bad cramps. Many of them I think are helped by diuretics, but I wonder as diuretics, is it the diuretic or is it something else that you are really doing for them? And I am not quite sure that we got an answer to that part of the question.

DR. FISCHER: I think many of these women are quite sensitive about the bodily changes that occur in the course of the menstrual cycle. Theresa Benedict did some work on this, and many women can feel when they are ovulating and many women can predict almost immediately as they approach menstruation. They get quite attuned to the bodily sensation and unquestionably all these bodily sensations do have disturbances and changes both physiologically and pathologically in a variety of these endocrine and chemical balances. I would say that it seems to me, though, a sine que non has to be a fear and a conflict in the approaching cycles that go along with them.

So I would say that irrespective of what symptoms you treat to return the body to more normal functions, where there is fluid accumulation or what, I would like to do a little talking to them, too, in which case I would just try to make a rational therapy that treats both sympoms and causes, and if definite symptoms occur, then I am in favor of treating them, but at the same time adding a little talk and a realization that emotions about these things frequently and most often do play a pretty crucial part.

CHAIRMAN STERN: I think on this matter of premenstrual tension — do you have anything to say on this, Dr. Fitchett, what you have done with them?

DR. FITCHETT: No, other than to say I think it is just as much a problem as dysmenorrhea, and very frequently in these cases edema is a factor in causing their discomfort, and by relieving their edema, along with the talk Dr. Fischer would give them, I think we do help them each period.

I think it is important to treat their symptoms, and I think that the symptoms of premenstrual tension are probably easier treated and more readily helped by medication than they are in dysmenorrhea.

CHAIRMAN STERN: Dr. Rakoff, do you have anything specific to say about your treatment of this condition?

DR. RAKOFF: Dr. Dewees, one point I did want to make is that of course not all patients with premenstrual tension have dysmenorrhea, nor do all patients that ovulate have dysmenorrhea. That is the whole crux of the situation. Why do some patients who have normal ovulatory cycles have dysmenorrhea and others who are apparently equally normal endocrinologically don't? That is why I said before that we don't know the true endocrine answer to dysmenorrhea. There is something there that ovulation facilitates, but we don't know what it is because it is present in some women and not in others.

So far as premenstrual tension is concerned, I think that the majority of these patients can be helped by a salt-poor diet in the premenstrual phase plus diuretics, as Dr. Fitchett pointed out, either ammonium chloride, Diomox, Neohydrin, or Neo Bromth. Some patients respond better to one, some better to the others.

Now, with a patient with sort of intractible premenstrual tension which does not respond to these measures, which is unusually severe, and there are patients who gain as much as eight pounds in the premenstrual phase, these people are often benefitted by 10 milligrams of methyl testosterone for ten days before their period.

CHAIRMAN STERN: Thank you, Dr. Fitchett and Dr. Fischer.

DR. LEVINSON: Dr. Rakoff twice stressed the fact of giving estrogens every other month. What about the patient with severe endometriosis that might be treated by the Karnaky regime of giving progressively large doses of estrogen over a period of

some months? Am I correct in assuming you are definitely opposed to that?

DR. RAKOFF: I personally don't like estrogen therapy for the treatment of endometriosis, because this is based on the fact you are first stimulating the endometrium and then exhausting its ability to respond. So before the patient gets better she has to get worse. And I have run into too many problems during the stage in which they are getting worse. You have to give the estrogen continuously there and you can't discontinue it. Once you discontinue you are in trouble. The patient begins to bleed, the endometriosis flares up. You have to inhibit the cycle by giving estrogen in large doses over a long period. I prefer androgen for this purpose, giving it cyclic fashion. Keep the endometriosis in control over a young woman where you want to be conservative. More recently we have had some interesting experience with the new progsterone compounds; they are giving it continuously inhibiting the cycle. We haven't gotten into any difficulty. We have been giving 20 to 30 milligrams of Noritin in a day, and we seem to be getting very encouraging results. But it is a little too early for me to say.

CHAIRMAN STERN: I want to thank Dr. Fitchett, Dr. Fischer and Dr. Rakoff for coming down here and giving us this interesting discussion, and I would like to thank the audience for entering into this discussion.

SAFE KEEPING OF MEDICAL CREDENTIALS

The services of a Central Repository for Medical Credentials became available July 1, 1958 to doctors all over the world. Many doctors today are unable to utilize their professional skills because of the loss or destruction of their original credentials. The World Medical Association undertook this program to assure that the doctor will always be able to prove himself medically trained and fully accredited to practice medicine.

Lifetime cost of this service to the newly graduated doctor in the United States is approximately $60.00 on a one-payment basis. An actuarial schedule has been established for doctors in various age groups. A ten-year service rate is also available.

Repository officials suggest that the credentials deposited should include official medical school record, medical diploma and specialist credentials. Doctors should NOT send their original credentials, but should send photostatic, microfilm or notarized copies of their original credentials.

Forms and additional information are available from The World Medical Association, 10 Columbus Circle, New York 19, New York.

● This article is based on an investigation of the records of individuals from the three institutions who have been adjudged delinquent. It does not assume that a truly representative random sample of the population at large is involved but provides some information regarding reading disability among this select population.

A NORMATIVE STUDY

OF READING DIFFICULTY IN DELINQUENTS

LEON PETTY, M.S.*

A considerable proportion of the adolescent population examined at the Mental Hygiene Clinic have been involved in some type of activity which may be designated as delinquent in nature. This delinquent behavior covers a variety of transgressions against the social pattern and undoubtedly is multicausal in origin. Many institutions, i.e., family, school, etc., play a dynamic role in the socialization of the individual, thus helping him to adapt to his environment. However, personal and social maladjustment of the child is intimately linked with his emotional adjustment.

Reading Deficiency a Link

In examining adolescents referred by institutions because of delinquent behavior, it becomes obvious that many of them experience a similar problem, namely reading deficiency. In effect they are or have been laboring under some disturbing emotional stress which has hampered social adjustment and which may or may not have precipitated an attempt to find other avenues of achieving satisfaction.

The nature of the emotional stress experienced by a child beginning school are enormous, yet many adjust or adapt readily to the procedures. Why, then, do some children become behavioral problems, while others adjust with a minimum of conflict? Again a multicausal approach seems to be the answer—with environmental background, personal adjustment and the school curriculum as partial reasons for failure. Some children approach school entrance with confidence, poise, cheerfulness and a cooperative attitude while others are relatively immature emotionally. They are timid, shy, self-centered, un-cooperative in routine school activities, unable to get along with others and are easily upset emotionally. Thus, inadequate emotional stability, insufficient self-reliance and inability to cooperate, may handicap a child in his effort to learn to read. However, emotional factors alone are not the only reasons for

*Clinical Psychologist of the Mental Hygiene Clinic.

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1. Innerfield, I.: Clinical report cited with permission
2. Clinical report cited with permission

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severe bruises ... swelling ... cleared by fifth day[2]

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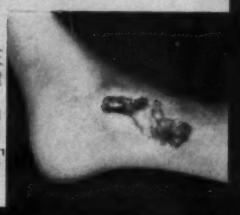
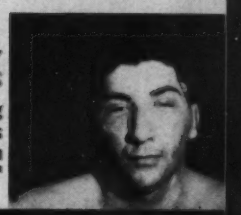


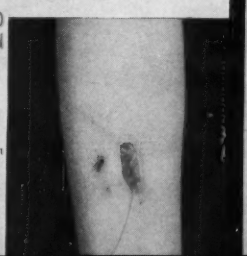
INFLAMMATORY DERMATOSIS

rapidly spreading rhus dermatitis healed within a week[1]



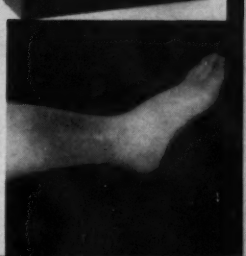
INFECTED LACERATION

marked reversal in 3 days... returned to school... closure advanced[1]



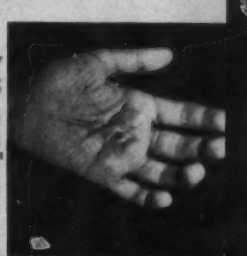
THROMBOPHLEBITIS

back on his feet in a week after recurrent episode[1]



REFRACTORY CELLULITIS

normal routine resumed after 4 days of VARIDASE[1]



reading disability. Other factors, i.e., intelligence, physical, social and educational may affect the child in his effort to learn to read. This inability to learn to read leads to frustration which may be manifested in a variety of ways.

The Vicious Circle

The severe frustration experienced by the child in his unsuccessful effort to learn to read makes him conspicuous in a socially unfavorable way—he is hurt and ashamed. The continued lack of success with concomitant and a feeling of insecurity may bring on emotional maladjustment. A particular child may develop feelings of inferiority, i.e., feeling of being stupid which may be enhanced by the attitudes of classmates, parents and even teachers, if they fail to understand the true situation. Reading and school activities become disliked and the child seeks opportunities to avoid it. A variety of techniques may be employed, such as—becoming withdrawn, indulging in excessive daydreaming, developing nervous habits (i.e., nail biting or appearance of hysterically motivated illness) or compensation for feeling of inferiority in the form of antisocial behavior.

Mean difference between reading achievement actual grade placement and estimated reading expectancy (theoretical grade level):

Results

The subjects achieved intelligence quotients ranging from the borderline level of intelligence to the superior level of intelligence. Table one gives a distribution of the quotients by sex.

Table I—Intelligence Quotients

	70-79	80-89	90-109	110-119	120 & Above	
Male	7	6	16	1	2	=31
Female	6	1	11	1		=19
	13	7	26	2	2	50

Table two summarizes the mean difference between the actual grade placement and the achievement and theoretical grade level.

The sample consists of 50 cases of children ranging in age from 8:4 to 16 years of age. They were selected at random from subjects under the auspices of the Youth Service Commission. All had been administered some form of intelligence test and the Wide Range Achievement Test.

The reading grade achieved on the achievement test ranged from 1.4 to 11.1, while the actual grade completed in school ranged from grade 2 to 11. However, the expected grade (theoretical grade) yielded a range of 3.2 to grade 12.8. The mean difference between the actual grade placement of the achievement test grade varied from 0.3 to 6.0 grades of reading disability. The discrepancy between the grade placement and the theoretical grade varied from 0 to 9 years of reading retardation.

The significance of the above results indicates that over half of the sample show a significant discrepancy (more than 1 year of reading retardation) between the achievement test grade and the actual grade placement. This discrepancy becomes accentuated when one considers the grade expected of the individual (based on the number of years in school) and the grade placement. In the latter case, approximately 90% of the sample show more than 1 year of reading retardation. Although the intellectual level (other conditions being equal) of the individual affects his reading ability, the variation for the population sampled was greater in those subjects with average than those with below average intelligence—even though most of the latter group were placed in grades above their achievement level. As could be expected, subjects with above average intelligence showed the least

TABLE *II*

No. of Yrs. Retarded	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
Achievement Test Grade	15	10	10	3	10	1	1	0	0
Theoretical Grade Level	5	8	6	6	6	8	4	6	1

amount of variation between actual, achieved and theoretical grade. The disability, although varying with intelligence, is widespread for the group studied and perhaps more prevalent in boys than in girls.

Although a large proportion of the sample achieved intelligence quotients below the average range, their actual and expected grade levels reflect their inability to learn to read which differed from the average and above average only in the respect that the latter group showed a greater range than the former in terms of retardation. With increasing levels of retardation, greater frustration and acting out behavior was exhibited by the group with average and above average intelligent quotients.

In the beginning of this article, mention was made of the role of the family in the socialization of the child. Information gathered from the records indicates that 75% of these idividuals studied are products of broken homes, clearly illustrating the assumption.

SUMMARY

Fifty records of children placed in institutions because of delinquent behavior have been examined psychologically with the following results:

1. The vast majority show a typical pattern of reading disability.
2. Discrepancy between expected grade and achievement grade varies from 0 to 9 grade levels of reading retardation which shows a greater amount of retardation than the discrepancy between actual and achieved grades.
.3 Discrepancy between those of below average I.Q. is not as great as that for average and above average I.Q.
4. There appears to be strong indications of a positive correlation between home milieu or condition and learning disability.

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THE PHYSICIAN AND THE PUBLIC SCHOOLS

It is well worth the private physician's time to consider the results of school testing and evaluation procedures. A child seen infrequently for organic illness may be understood in a quite different light when such results, arrived at by people seeing the child daily over a period of years, are given due weight. . . .

. . . . As physicians, we need to be aware of the health and paramedical programs designed to improve the scholar's total school and community adjustment. If services are lacking, if particular school systems are failing to offer speech and hearing training and sound psychological and guidance services, physicians should take an active part in furthering the development of these areas in their respective communities. Active participation on school health councils, or in P.T.A. or other activities by private doctors can aid immeasurably in securing needed special services.—Norman C. Chaucer, M.D., in Connecticut Medicine.

● **Diagnosis and successful therapy is often difficult in this stubborn condition, frequently found in patients. The author recommends Trypsin troches as an adjunct to treatment in obstinate cases.**

CHRONIC POSTNASAL DISCHARGE

ABRAM H. PERSKY, M.D.*

Chronic postnasal discharge, or postnasal drip, as it is more commonly termed is one of the most frequent and troublesome complaints seen by the physician. This drip may be purely on a physiologic basis as a natural result of the normal physiologic action of the cilia, in their capacity of sweeping backward and downward into the posterior nasopharynx, any bacteria, dust, foreign bodies, powders, or any other substances that may be inhaled. However, just as there are degrees of the amount of postnatal discharge, so are the symptoms in direct proportion to the amount discharged. There are also many characteristics to the discharge which require a careful consideration, both from the standpoint of prognosis and of treatment. A true simple postnasal discharge is nonpathologic and normal to a degree. However, this discharge may have developed purulent characteristics which speak of an infective process somewhere in the upper respiratory tract. In consequence, this type of a discharge may have some pathologic significance not only from a local standpoint, but also from systemic reactions.

To better understand the modus operandi of the postnasal discharge, it is important to review the physiology of the mucous membrane of the nose. There are two primary functions of the nasal mucosa, namely, to humidify the inspired air and to warm it to the proper temperature, so that when it reaches the posterior pharyngeal spaces and the lungs, it is non-irritant and can be tolerated by the lower respiratory areas. Passage of inspired air through the nasal cavity from the nares to the posterior choanae required less than ¼ of a second. When it reaches the pharynx, the relative humidity of the inspired air is about 75% or more. The turbinates are well adapted to the function of radiating heat, thus the inspired air is warmed by the nasal cavity up to a temperature between 36 and 37 degrees C.

The amount of water secreted by the nasal cavity in each 24 hours is close to one quart. The mechanism by which moisture is supplied to the inspired air is still subject to speculation. Some investigators believe that the moisture is supplied by the nasal secretions, while others maintain that it is supplied by a serous exudate from the capillaries and the vessels of the mucous membrane. The cilia have a mucous blanket which, due to the ciliary activity, in a gen-

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eral way moves backwards towards the nasopharynx. This blanket is adapted to trap dust, bacteria, powder, etc. and it carries these foreign bodies at various speeds to the nasopharynx.

Various factors can act to either accelerate or delay the movement of the cilia. Environmental factors, emotional disturbances, various types of irritants that may be inspired, various medications that may be taken either internally or applied locally, all can have an influence on the rapidity of this ciliary action. Slowing the ciliary motion would normaliy cause a stagnation of bacteria and foreign particles on the mucous membrane of the nose. This, in turn, would cause a greater opportunity for an absorption of the toxic substances into the blood stream of the mucous membrane and a development of a purulent process. Certain pathologic conditions in the nose and throat, and certain systemic conditions may have either a direct or indirect influence on the normal function of the cilia. Among these, one may state anatomic malformations, such as a marked deviation of the septum, wherein there is so much narrowing of one nostril, that the inspired air on that side does not have a proper opportunity to reach the turbinates and, consequently, cannot be moistened nor warmed with the result that foreign organisms or foreign matter that may be present on the cilia, do not have an opportunity of being driven back into the nasopharynx. In the other nostril, there may be an increased patency due to the marked concavity of the septum with the result that too much air is inspired from this nostril, and in consequence, there is the drying of one side of the pharynx.

Postnasal discharge may be the result of acute or chronic sinus disease. It may be the result of a hypertrophic rhinitis. It is often seen in cases of atrophic rhinitis. The presence of diseased tonsils and adenoids very frequently gives a purluent postnasal discharge with the sensation of hawking and coughing. Allergic states are important. True allergy of the nose rarely produces a simple postnasal drip. However, due to the marked congestion of the mucous membrane of the nose during an allergic state, there usually is associated a more or less purulent discharge due to the stasis of the cilia and a secondary infection.

Infected lymphoid tissue in the nasopharynx is an extremely important source of this postnasal discharge. This is particularly true in adults where there may be islands of hypertrophied lymphoid tissue either on the posterior pharyngeal wall, in the nasopharynx, or a hypertrophy of lymphoid tissue on the base of the tongue. Small residual tonsillar tabs may maintain a chronic infection and add to a chronic postnasal drip. Other causes that seem to influence a postnasal drip may be the excessive use of alcohol and tobacco, improper diet, and very often inadequacy of rest. Systemic influences, such as diabetes, malnutrition and hormonal imbalances have been associated with this condition. There may be other causes such as smoke, dust, various types of fumes, odors, extreme temperature changes, various types of plastic materials that are being processed in various areas, all have an influence on increasing the postnasal drip. Drugs have also a direct relationship, particularly, the newer preparations that have been used by the hypertensives, such as serpasil, etc.

Symptomatology

The common symptom is that of hawking, or sensation of either a lump in the throat, or of swallowing a discharge, a marked cough, very frequently in the morning, with or without expectoration, irritation of the throat, choking sensations, and frequently hoarseness. Strenuous hawking and attempting to remove this plug of mucous may occasionally produce a certain amount of blood spitting. Nausea and vomiting is not an infrequent complaint. The discharge may be either purulent or non-purulent.

Diagnosis

It is often extremely difficult to establish either the diagnosis or the etiologic fac-

tors that present this symptom. In spite of a detailed examination, frank abnormality is often absent. To supplement a careful and detailed history, the following procedures are in order:

Anterior rhinoscopy with nasopharynscopy, posterior rhinoscopy, transillumination of the sinuses to be supplemented by roentgen examination. A mirror laryngscopy will reveal important findings, both on the dorsum of the tongue, the supra glottic, and the laryngeal areas. It is important to rule out the presence of a Thornwald's bursa, lymphoid masses on the posterior pharyngeal wall or on the dorsum of the tongue, the presence of diseased tonsils of tonsillar tabs and residual masses of adenoid tissue.

In addition, the local findings are often inconclusive, and a recourse to a detailed medical review is indicated to evaluate the influences of either systemic, environmental, emotional or other functional factors that may have either a direct or indirect influence on the patient.

Treatment

Treatment must be directed to the underlying pathology—measures employed will include: 1) conservative medical treatment to the nose and throat; 2) surgical measures; 3) radiation; 4) systemic measures and 5) Trypsin.

Conservative medical treatment is indicated in acute and chronic sinus pathology, hyperplastic ethmoiditis, and atrophic rhinitis. Intra-nasal medication should be of a bland, non-irritating nature whose pH is that of the normal nasal secretions. The medication may be administered either in the form of drops, sprays or by the displacement method. The addition of the antibiotics to the solution is of questionable value. In cases where there is a moderate proliferation of lymphoid tissue on the pharyngeal wall, local application of a 2-5% silver nitrate solution may be beneficial. Gargles are of little value, but may have a psychological effect. Certain drugs such as iodides or ammonium chloride taken internally may help liquefy the secretions and so reduce the severity of the symptoms.

Surgical measures include antral lavage, polypectomy, a partial middle turbinectomy, the removal of mulberry growths on the posterior ends of the turbinates, submucous resection, excision of a Thornwald's bursa, tonsillectomy and adenoidectomy, excision of the recurrent lymphoid tissue in the nasopharynx, in the pharynx, or on the dorsum of the tongue.

Roentgen therapy: This form of therapy has limited value and when used extreme care must be exercised since late side effects have been reported. It can supplement surgery in cases of extensive lymphoid hyperplasias.

Systemic medication should be directed to control diabetes, correct metabolic disturbances, hormonal imbalance, and malnutrition. Attention should also be directed to the diet, excesses of alcohol and tobacco, and any environmental or emotional states that may be present. Allergy, if present, should receive intensive anti-allergic treatment.

A number of cases of chronic purulent discharge exhibit only a lymphoid hyperplasia. In spite of the therapeutic measures outlined above, the results were unsatisfactory. In reviewing the literature, it was found that Trypsin* given parentally had a beneficial action in liquefying the secretions in cases of chronic bronchitis, bronchiectasis, and asthma. In consequence, a special troche was prepared containing Trypsin 1.0 mgm., Benzocaine 5.0 mgm., Neomycin sulphate 5.0 mgm. and zinc Bacitracin** 50 units.

These troches were administered to a group of 19 patients, who presented a history of chronic purulent postnasal discharge of varying duration and severity. The associated symptoms included hawking especially on arising, cough, tightness and irritation in the throat, and often a choking sensation. The patients were all in the older

*Parenzyme Aqueous (National Drug Company).
**National Drug Company.

age group. Frank sinus abnormality was absent in the entire group. With one exception, they all presented varying degrees of a chronic nasopharyngitis with a lymphoid hyperplasia in the nasopharynx, pharynx or on the dorsum of the tongue.

TABLE I

No.	Name	Age	Sex	Symptom	Diagnosis	Dose	Results	Comments
1	W.	46	F	Postnasal drip, choking sensation, cough.	Chronic naso-pharyngitis	1 q 4 hrs.	Poor	No improvement after 2 weeks—no side reactions.
2	G.	57	M	Postnasal drip, lump in throat.	"	"	Good ++	Much improvement—no side reactions.
3	P.	62	M	Postnasal drip, cough in A.M., tightness.	"	"	Good ++	Improvement—mucous freed—cough absent—no reactions.
4	H.	60	M	Choking sensation, postnasal drip, hawking.	"	"	Good ++	Marked improvement—drip less—no hawking—no side reactions.
5	R.	53	F	Postnasal drip, cough in A.M., and at bedtime.	"	"	Good ++	Improvement after 2 weeks—no side reactions.
6	A.	54	M	Cough, choking sensation, postnasal drip.	"	"	Good ++	Much improved—no side reactions.
7	O.	64	F	Postnasal drip, tight in throat.	"	"	Good ++	Loosened discharge—no side reactions.
8	P.	60	F	Postnasal drip, hawking in A.M., thick plug.	"	"	Good ++	Loosened secretion— no cough—no reactions.
9	R.	55	F	Postnasal drip, cough.	"	"	Poor	No improvement after 2 weeks—no side reactions.
10	H.	61	F	Postnasal drip, cough, hawking.	"	"	Good ++	Slightly dizzy—took Rx too often.
11	A.	51	F	Postnasal drip cough A.M.	"	"	Good ++	Much relieved—no side reactions.
12	C.	59	F	Postnasal drip, cough especially A.M.	"	"	Good ++	Marked improvement—lessening of discharge—no side reactions.
13	B.	45	F	Postnasal drip, choking sensation.	Vasomotor Rhinitis	"	Poor	Developed nausea—stopped Rx after 3 days.
14	R.	49	F	Cough, tightness in throat, Postnasal drip,	Chronic naso-pharyngitis	"	Good ++	Marked improvement—1 week—no side reactions.
15	S.	36	M	Postnasal drip. cough expectoration.	"	"	Good ++	Loosened secretion—no cough.
16	McD.	70	M	Postnasal drip, cough expectoration.	"	"	Good ++	Marked improvement—drip less—no side reactions.
17	J.	55	F	Hawking, cough expectoration.	"	"	Good ++	Loosened secretion—no cough after 2 weeks—no side reactions.
18	S.	52	F	Postnasal drip, cough expectoration.	"	"	Good ++	Discharge less—no cough 2 weeks—no side reactions.
19	C.	41	F	Postnasal drip, cough expectoration in A.M.	"	"	Good ++	Secretion loosened—no cough after 2 weeks—no side reactions.

Unless otherwise specified, duration of therapy was one week.

The Trypsin troches were administered every four hours for a period of one to two weeks. Sixteen of the nineteen patients reported excellent results, namely, the secretion became looser, the cough disappeared, they felt greatly relieved of their symptoms and did not have any frank side reactions. Three patients had to terminate the treatment, two because of nausea, which developed on the third day of treatment, and the third failed to show any improvement after two weeks.

It is felt that the Trypsin in the troche had an effect of causing a liquification of the fibrin and mucous secretions. The Neomycin and Bacitracin exert a bacteroistatic action, and so reduce the irritative nature of the discharge. It was also noted that after a course of treatment, the lymphoid masses appeared smaller, and even disappeared in certain areas.

Conclusions

1. Chronic postnasal discharge is due to numerous anatomic physiologic and pathologic factors that make both diagnosis and successful therapy very difficult.

2. Attention to the sinuses, the nose, the nasopharyngeal space, the pharynx, tonsils and the base of the tongue is of prime importance.

3. Systemic conditions such as metabolic disturbances, hormonal imbalance, allergic states, emotional disturbances, and environmental influences must be evaluated and corrected.

4. Therapeutic measures should include intra-nasal medication, displacement therapy, antral-punctures, surgery, if indicated, the antibiotics and all other necessary adjuvants.

5. As an addition to the many therapeutic measures, Trypsin troches are recommended in obstinate cases, where there is the thick purulent type of secretion, and where one finds the hypertrophic lymphoid patches either in the nasopharynx, the pharynx, or about the base of the tongue.

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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ANEMIA*

● Anemia should always be regarded as a danger signal demanding careful reevaluation of the patient's general condition. It is a symptom which should never be accepted as a diagnosis. The author continues his comprehensive outline on the subject.

ANDREY GEORGIEFF**

TABLE VII

CLASSIFICATION OF MALABSORPTION SYNDROMES

I. Primary malabsorption (primary sprue)

A. In children
   1. Celiac disease

B. In adults
   1. in tropics: tropical sprue
   2. In temperate zone: nontropical true (idiopathic steatorrhea)

II. Secondary malabsorption (secondary sprue)

A. Infiltrative disease
   1. Enteritis
      a. Idiopathic.
      b. Tuberculous
   2. Intestinal lipodystrophy (Whipple)
   3. Amyloidosis, scleroderma, etc.
   4. Tumors
      a. Hodgkin's disease
      b. Lymphosarcoma

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

B. Congenital or surgically produced anomalies
   1. Blind loops
   2. Extensive resections of small bowel
   3. Subtotal or total gastrectomy
   4. Fistulas

C. Endocrine disorders
   1. Adrenal insufficiency
   2. Pituitary insufficiency

III. Error of Digestion

A. Pancreatic disease
   1. In children
      a. Cystic fibrosis
   2. In adults
      a. Pancreatitis
      b. Carcinoma
      c. Surgical resection

B. Biliary tract disease (malabsorption usually minimal)
   1. Intrapatic: cirrhosis of any type
   2. Extrahepatic: common duct obstruction from any cause

In a patient with anemia, in order to determine the possibility that the anemia might be hemolytic, order the following:

Icterus Index (7), *Fecal Urobilinogen* (8), *Urine urobilinogen* (9), Total serum bilirubin — direct and indirect (10), test for free Hb. in the blood and *hemoglobinuria* (11). In hemolytic anemia 7, 8, 9, 10 and 11 are increased. Details will be given further under Hemolytic anemia.

12. *Osmotic Fragility Test.* When normal red blood cells are mixed with descending concentration of hypotonic salt solution, some of the red blood cells undergo hemolysis within the range of 0.48-0.40% Sodium chloride and there is complete hemolysis at 0.3% Sodium Chloride. In hereditary spherocytic anemia (hereditary spherocytosis) there is partial hemolysis in concentrations above 0.40% sodium chloride that is here the osmotic fragility is decreased. In Thalassemia, Sicklemia and obstructive jaundice, hemolysis occurs at levels lower than the control (that is at levels lower than normal). That is here the osmotic fragility of the red blood cells is increased.

13. Test for *mechanical fragility* of red blood cells. Increased mechanical fragility has been observed in congenital hemalytic jaundice, in sickle cells anemia, and in the presence of cold agglutinins, as well as in a few cases of atypical hemolytic anemias in

*The first section of Part II appeared in the November issue.
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which osmotic fragility was normal are decreased.

14. *Survival time of red blood cells.* Normal red blood cells when transfused into normal recipients exhibit a survival of about 120 days, with a linear slope of disappearance. The survival time of red blood cells may be measured by the method of Ashby, but the easier method of studying the survival of patient's or donor's cells tagged with radioactive chromium.

15. *Warm antibodies* are antibodies which act maximally at 37C. They act as incomplete antibodies. They occasionally act as "complete" agglutinating antibodies and under certain circumstances may cause hemolysis. Although the number of possible causes of hemolytic anemia is large, as the table of Etiologic classification of anemia shows, in a very significant number of cases of acquired hemolytic anemia no cause is found and no associated disease is recognized. These cases are included as idiopathic cases. However, in the majority of idiopathic hemolytic anemias a "warm antibody" is present and the test for warm hemolysin is positive; i.e., the antibody reacts well at 37 degrees C. and is not potentiated at a lower temperature. The most common warm antibodies are "incomplete" that is, they sensitize normal red blood cells to antiglobulin serum but do not cause agglutination in a saline medium.

16. *Test for Cold Hemolysin.* "Cold" antibodies are markedly potentiated by reducing the temperature below 37°C. These antibodies are "incomplete" antibodies but they may also act as "complete" antibodies. There are two tests for demonstrating cold hemolysin: one is presumptive (technically easy test) and the other is done when the presumptive test is positive. This other test is the Donath-Landsteiner test and is more complete (but technically more difficult to perform).

"Cold" antibodies have been demonstrated in paroxysmal cold hemoglobinuria and in some acquired hemolytic anemias. In cases of acquired hemolytic anemia associated with the presence of cold antibodies, cyanosis and Raynaud's phenomenon on exposure to cold as well as hemoglobinuria may be noted.

(In addition to these warm and cold autoantibodies, it is not uncommon to find other manifestations of abnormal protein formation in patients with acquired hemolytic anemia. Thus antibodies may be formed which give false positive Wasserman and Kahn reactions.)

17. *Test for Increased Acid Hemolysis.* This test is positive in paroxysmal noctur-

TABLE VIII. COOMBS' TEST

Hemolytic disorder	Antihuman globulin serum mixed with patient's R.B.C. (direct Coombs' tests)	Antihuman globulin serum mixed with normal RBC after incubation in patient's serum (indirect Coombs' test)	
		Rh+	Rh—
A. Acquired hemolytic anemia:			
1. With circulating antibodies	+	+	+
2. Without circulating antibodies	+	—	—
3. Due to erythroblastosis fetalis	+	+	—
4. Due to physical or chemical agents	+ —	—	—
B: Congenital hemolytic anemia (hereditary spherocytosis)*	—	—	—
C. Sickle-cell anemia	—	—	—
D. Paroxysmal nocturnal hemoglobinuria	—	—	—
E. Cold hemoglobinuria (type associated with syphilis)	+	—	—

* The occasional finding of a positive Coombs' test in this and in other hemolytic anemias where the test is usually negative is explained by superimposed, frequently transient, episodes of acquired hemolytic anemia.

nal hemoglobinuria. The test is performed by putting the red blood cells in a slightly acid pH with CO_2. The test is positive if hemolysis of the red blood cells appears.

18. *Coombs' Test.* The most commonly employed serologic (immunologic) test is the Coombs' test (or also called antiglobulin test.) The direct Coombs test demonstrates the presence of "incomplete" antibodies; that is, those which are attached at some points on the surface of the red blood cells and require a completing substance, such as antihuman globulin, to cause an agglutination reaction to take place. The direct Coombs' test is carried out simply by mixing the patient's washed red blood cells with serum from rabbits immunized to human gamma-globulin and examining the mixture for agglutination. A positive reaction has been observed in cases of idiopathic acquired hemolytic anemia, in that type of paroxysmal cold hemoglobinuria which is associated with syphilis, and in many instances of "symptomatic" hemolytic anemia. The test is negative in most cases of hereditary spherocytosis and is generally negative in sickle-cell anemia and in paroxysmal nocturnal hemoglobinuria, but in hemolytic anemia due to various physical or chemical agents it has sometimes been positive. A positive direct Coombs' test is also observed when isoimmunization to unknown immune bodies has occurred, as in hemolytic disease of the newborn and in sensitization following transfusion. The "indirect" Coombs' test serves to differentiate such antibodies. In the "indirect" test, antihuman globin serum is mixed with normal group O, Rh-positive, and Rh-negative red blood cells which have been incubated in the patient's serum.

The resulting reactions are shown in the table below. If agglutination occurs with both Rh-positive and Rh-negative cells, Rh antibodies can be excluded.

19. *Wasserman* — Some hemolytic anemias cause positive Wasserman.

20. *Sickle-Cell Preparation* — Details are discussed under "Sickle cell anemia."

21. *Hemoglobin Electrophoresis* — Hemoglobinopathies other than Sickle-cell anemia and Thalassemia can be diagnosed only by electrophoretic studies of the hemoglobin. Only by electrophoretic studies of the hemoglobin can we find if a hemolytic anemia is due to an abnormal hemoglobin in the red blood cells. (Hemoglobin C, D, E, G, H, I, J and K.)

Two techniques are used for the routine Hb. analysis, alkali denaturation and paper electrophocesis. It is to be noted that these tests are not always conclusive and that occasionally other techniques are necessary for final diagnosis of the patient's Hb. type. The two techniques mentioned above are simple and inexpensive and may be performed in any laboratory. Remember that blood for the above two methods should be obtained prior to any transfusion; otherwise they are of little value. If the alkali denaturation and/or paper electrophocesis do not give information about the exact time of the patient's Hb., other methods may be used, but they are done in special laboratories because they are difficult. These other tests are starch block electrophoresis, tiselius metal, and others.

21. *Coagulation time, clot retraction, prothrombine time, bleeding time, prothrombin consumption test, and test for fibrinogen deficiency.* In which diseases each of the above tests is abnormal is listed in Table IX and Table X.

TABLE IX

CAUSES FOR ALTERATION IN THE VARIOUS TESTS OF COAGULATION

I. Positive tourniquet test

A. Thrombocytopenic purpura — platelets too few to support capillaries under pressure
B. Nonthrombocytopenic purpuras — damage of capillary endothelium
C. Scurvy — deficiency of intercellular cement substance
D. Scarlet Fever
E. Uremia

II. Prolonged Bleeding Time

A. Thrombocytopenic purpura

B. von Willebrand's disease — abnormality of capillaries
C. Any of the causes under III and V — due to extreme poverty of coagulation factor

III. Prolonged Coagulation Time

A. Deficiency of AHG
B. Deficiency of PTC
C. Deficiency of PTA
D. Deficiency of Hageman factor
E. Deficiency of fibrinogen
F. Deficiency of prothrombin and/or proacelerin and proconvertin if deficiency is severe.
G. Idiopathic — unknown anticoagulants

IV. Poor Clot Retraction

A. Thrombocytopenia from any cause
B. Thrombasthenia — platelets numerically adequate but functionally inadequate.

V. Prolonged Prothrombin Time

A. Deficiency of prothrombin
B. Deficiency of proacebrin
C. Deficiency of proconvertin
D. Combination of A, B, and C.

VI. Reduced prothrombin consumption

A. Deficiency of AHG
B. Deficiency of PTC
C. Deficiency of PTA
D. Thrombocytopenia
E. Thrombasthenia
F. Circulating antithromboplastin

The above may be expressed in a different way of classification:

TABLE X

CLASSIFICATION OF THE HEMORRHAGIC DISEASES

1. Vascular abnormality:
   a. abnormal bleeding time
   b. abnormal capillary fragility
   c. all other tests normal
2. Platelet defects (quantitative or qualitative)
   a. Abnormal tests as noted in 1 above and 3 below
3. Deficiency of one of the elements of the Thromboplastin group
3a. Presence of a heparin-like agent
   a. Coagulation time abnormal
   b. Prothrombin time normal
   c. Prothrombin consumption test abnormal
4. Deficiency of one of the elements of the prothrombin group
4a. Presence of antiprothrombin or dicumerol-like agent
   a. Prothrombin time abnormal
5. Deficiency of fibrinogen
5a. Presence of a fibrinolytic agent
   a. Poor clot, no clot, or clot is lysed.

23. *Serum iron content.* Is reduced below normal in cases of iron deficiency; may be reduced in association with the anemia of chronic infection, and in various types of anemia in which blood regeneration is active. The determination of serum iron and iron-binding capacity is frequently helpful in differentiating iron deficiency anemia from one of the inherited hypochromic disorders. These tests are quite difficult and can only be performed by competent technicians. A frequent error is the performance of the serum iron level only, without the iron-binding capacity, the latter being technically the more difficult determination of the two. The serum iron level shows marked normal variations, and it is of extreme importance to know the percent saturation of the iron-binding globulin if these tests are to be used for evaluation of a patient's status. Serum iron content is increased in P.A. in relapse and in hemolytic anemias. However, the increased plasma iron of P.A. in relapse falls to values below normal during the time when blood regeneration is occurring as the result of specific therapy.

24. *Iron binding capacity of the plasma.* An interesting difference between the findings in cases of iron deficiency and in those caused by infection is that the iron binding capacity of the plasma is greatly increased above the normal when the hypoferremia is due to iron deficiency, whereas it is less than normal when the hypoferremia is associated with the anemia of chronic infection.

25. B.M.R., P.B.I. and blood cholesterol

for determination of thyroid function, because myxedema may cause anemia. This is usually normocytic, but can be macrocytic.

26. Total serum protein, albumin and globulin, or preferably protein electrophoretic studies.

27. Liver tests (BSP, etc.) because liver diseases may cause anemia.

28. Occult blood in stools. Prior to sending stools for occult blood, the following precautions should be taken:

a. Meat-free diet
b. No green vegetables are to be included in the diet. (They contain enough iron to cause positive occult blood)
3. No iron preparations
d. No aspirin or drugs containing aspirin, because larger doses of aspirin cause enough irritation and bleeding from the gastro-intestinal tract to produce positive test for occult blood.
e. No brushing of the teeth, because this may cause enough bleeding to produce positive occult blood reaction.

The specimen should be taken from the middle of the stool. The reaction should be positive or negative for three tests befor being accepted as valid.

29. Gastro-intestinal tract X-ray studies, to rule out lesions that may be causing anemia.

30. X-ray of the chest may reveal unsuspected metastatic mediastinal enlargement.

31. Rectal examination and sigmoidoscopy cannot be neglected for they may yield the first indication as to the nature and cause of the anemia.

32. Pelvic examination may yield the first indication as to the nature and cause of the anemia.

33. Intravenous pyelogram — The kidneys must be given attention, for it is not unusual for hypernephroma to cause an obscure anemia.

34. Test for achlorhydria of the stomach. (Do this with Histalog, which is a better preparation than Histamin.) If you do not wish to subject the patient to insertion of stomach tube, do tubeless gastric analysis with dye "Diagnex."

35. Roentgenograms of the bones may lead to the discovery of tumors or of periosteal elevations suggesting leukemia.

36. Evaluate adrenal function, because adrenal disease or hypofunction may cause anemia. The simplest method is: Collect a 24 hour urine specimen for 17-ketosteroids (normal value for male 10-15 mg./24 hours, female 7--10 mg./24 hours) and for 17-hydroxycorticoids (normal values for male 4-8 mg./24 hours, female 3-6 mg./24 hours.) In Addison's disease, the anemia is normocytic.

37. Evaluate pituitary gland function if disease of the pituitary gland is suspected, because such disease can cause anemia. In pituitary insufficiency, the anemia is normocytic.

38. Bone marrow biopsy. In bone marrow examination, ask the laboratory for the following:

a. Is M:E ratio (myeloid:erythroid) increased?
2. Is there normoblastic hyperplasia?
c. Is there an increase of nonmyeloid cells?
d. Is there megaloblastic hyperplasia?

After obtaining an answer to the above questions from the pathologist, consult Table below, in which is given the bone marrow appearance in the various anemias:

a. *M:E raio increased:* 1. Myeloid forms of leukemia, 2. The majority of infections, 3. Leukemoid reaction, 4. Decrease in nucleated R.B.C.
b. *Normoblastic hyperplasia:* 1. Hemorrhagic anemias, 2. Iron-deficiency anemia, 3. Hemolytic anemia, 4. Thalassemia, 5. Cirrhosis of liver, 6. Polycythemia vera, 7. Plumbism, 8. Anemia of chronic renal disease.
c. *Nonmyeloid cells increased:* Other forms than myeloid leukemia, 2. Multiple myeloma, 3. Metastases from Ca., 4. Gaucher's disease, Niemann-Pick disease, aplastic anemia (usually relative increase only), infectious mononucleosis.
d. *Megaloblastic hyperplasia:* 1. P.A., 2. Malabsorption syndromes, 3. Macrocytic anemia with Diphyllobothrium in-

festation, 4. Megaloblastic anemia of infancy, 5. Megaloblastic anemia of pregnancy, 6. "Refractory" megaloblastic anemia.

39. *Siderocyte Stain of Blood Smear.* Siderocytes are red blood cells which contain granules containing iron, which appear as basophilic granules, when blood smears are stained with Wright's Stain. Siderocytes appear in the blood following splenectomy and may be seen in the blood of patients with unusual types of anemia.

Siderotic granules are normally present in the normoblasts of the bone marrow. The granules are not found in the normoblasts of patients deficient in iron.

40. *Stain of Blood Smear for Heinz Body.* Heinz bodies are irregular bodies, which are frequently observed in patients with hemolytic anemia, particularly in those caused by ingestion of toxic agents.

41. *Test for "L.E." Phenomenon.* This test is positive in disseminated lupus erythematosis. The test may be falsely negative when severe leukepenia is present. A negative test does not rule out the diagnosis of disseminated L.E. since in some patients with disseminated L.E. the test is negative. A unequivocably positive test is diagnostic of the disease. False positive rarely, if ever, occurs. (We said that L.E. can cause anemia.)

42. *Capillary Fragility Test.* This test is a crude measure of the capillary fragility. There is a fair degree of correlation between the number and size of the petechiae that appear during the performing of the test and the degree of thrombocytopenia. However, the test also depends on the fragility of the capillaries and may be markedly positive when the platelet count is normal. The test should not be repeated on the same arm until one week later.

I. Anemias due to increased loss of red blood cells

A. *Anemia due to acute loss of blood*

The immediate effects of hemorrhage depend upon the rapidity and amount of blood loss. Sudden loss of one-third of the blood volume may prove fatal, but as much as two-thirds may be lost over a 24-hour period without fatal outcome. The rapid loss of blood leads to reduction of blood volume, and the clinical manifestations are due mainly to low blood volume. If the blood loss is great, shock develops. If the patient survives the hemorrhage, the build up of the plasma volume leads to hemodilution that reaches full extent within 72 hours.

Laboratory Findings in "A":

1. Immediately after a hemorrhage, red blood cell counts, hematocrit and hemoglobin are normal, and no morphologic changes in the cells are found, since red blood cells and plasma are lost at the same time: the red blood count, hematocrit and hemoglobin are deceptively high. Within a few hours, fluid enters the circulation from the tissues resulting in hemodilution and a drop in the dead blood cell count and the hemoglobin proportional to the severity of the bleeding.

2. The resulting anemia is normocytic and normochromic, however, several days later, when the bone marrow commences to produce rapidly a large number of red blood cells to replace the lost, immature red blood cells are liberated from the bone marrow, and because these immature red blood cells are larger than the normal mature red blood cells, the anemia may become macrocytic normochromic. However, when the drain of the iron is greater than can be readily replenished, the anemia may become hypochromic.

3. Leukocyotses may take place within the first few hours following severe hemorrhage with "shift to the left." This is the first discernible blood change following acute hemorrhage.

4. The number of platelets increase.

5. Reticulocytosis appears several days after the hemorrhage. A persisting reticulocytosis forming a plateau-like curve, suggets that bleeding is continuing, for cessation of hemorrhage is marked by quick regression of the signs of stimulated hematopoiesis.

6. When the acute hemorrhage is internal, destruction of the blood and absorp-

tion of the products may lead to an increased excretion of urobilinogen in the urine and stools, and, rarely, even slight bilirubinemia may be found.

B. *Anemia due to chronic blood bloss*

In male the most common cause of chronic blood olss is bleeding (gross or occult) from the gastro-intestinal tract. In female the most common cause of chronic blood loss is excessive menses, this usually not being recognized by the patient nor the physician. The chronic blood loss drains the iron reserve and the critical factor here is iron depletion. The anemia is, therefore, strictly an iron deficiency anemia. When blood is lost in small amounts over a period of time, it appears that the bone marrow is not stimulated to replace the cells as it would be if the blood loss were more acute or of larger quantity. So the peripheral blood pattern of chronic blood loss combines the features of iron deficiency anemia with the signs of bone marrow suppression, or at least subnormal hematopoietic function. When massive hemorrhage complicates the course of chronic blood loss, the picture becomes one of iron deficiency plus active red cell formation. The laboratory pattern described below is the more common one of iron deficiency without release of new blood cells into the blood.

Laboratory Findings in "B":

1. The anemia is microcytic hypochromic.

2. *Blood smear.* The red cells are small and poorly filled with hemoglobin. Poikilocytosis is common. No polychromosia. No reticulocytosis. No nucleated red blood cells.

3. As a rule there is leukopenia with relative lymphocytosis.

4. The icterus index, serum bilirubin, fecal urobilinogen and urine urobilinogen are normal.

II. Hemolytic Anemia:

The symptoms in a hemolytic anemia depend upon the rapidity of hemolysis and its duration. Symptoms may be entirely absent or there may be a few manifestations The patient may complain of symptoms of anemia in general (see "Clinical features of anemia" in the November 1958 issue of this Journal). The patient may present, or may have had in the past, symptoms of hemolytic crisis. In chronic hemolytic anemia, splenomegaly is common and enlargement of the liver may be present. All grades, from acute fulminating disorders of several days' duration to entirely benign conditons of many years' standing, may be encountered. A chronic process may be interrupated by acute exacerbations. Jaundice is a sign common to all hemolytic anemias, but its degree may be such as to be barely perceptible, or so great as to be very striking.

In any patient with anemia, in order to determine the possibilty that the anemia might be hemolytic, order the following:

Icterus index (7)
Fecal urobilinogen (8)
Urine orobilinogen (9)
Total serum bilirubin (10)

In hemolytc anema, the values of (7), (8), (9), and (10) are increased, and this is evidence of increased erythrocyte destruction. In the same time the bone marrow will be producing r.b.c. with a rapid rate (increased rate of erythrocyte production) in an attempt to correct the anemia. In Table XI below, the diagnostic features of hemolytic anemia are given.

TABLE XI

DIAGNOSTIC FEATURES OF HEMOLYTIC ANEMIA

A. Evidence of increase rate of r.b.c. destruction:
1. Anemia
2. Hyperbilirubinemia (increased indirect bilirubin)
3. Increase in stool urobilinogen
4. Increase in urine urobilinogen

B. Evidence of increased rate of erythrocyte production:
1. Reticulocytosis
2. Polychromatophilia
3. Anisocytosis
4. Poikilocytosis

5. Nucleated red blood cells
6. Basophilic Stippling
7. Thrombocytosis
8. Leukocytosis (neutrophilia)

It must be kept in mind that a "compensated" hemolytic disorder (diseases) may be present. In this event the patient will not be anemic but there will be evidence of an increased rate of r.b.c. production and destruction. On the other hand, in many patients the survival time of the r.b.c.'s may be shortened only moderately and the bone marrow may be unable to produce cells at a sufficient rate to compensate for the mild anemia. In such patients there may be a mild anemia but the evidence of increased production and destruction will be minimal or absent. In these cases it may be necessary to measure the lifespan of the r.b.c. and to measure the rate of erythrocyte production.

Once it has been decided that one is dealing with a hemolytic disorder, then the various types of hemolytic disorders must be differentiated. The hemolytic disorders comprise a large group of conditions which vary as to their cause, pathogenesis, severity, duration, and treatment. The classification (that is the possible hemolytic disorders) were given in Table I.

The Following Tests are Used (Useful) in the Differentiation Between the Different Hemolytic Anemias:

See Table IV:

Tests Nos. 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 26, 27, 30, 33, 35, 36, 37, 38, 39, 40, 41, and 42

Van den Bergh (10) is of the indirect type, however, there may be also some increase of the direct Van den Bergh. Coombs' test (18) is positive in some hemolytic anemias.

When the degree of blood destruction is great, there is hemoglobinemia and hemoglobinuria and the urine is red. However, the finding of red urine must not be assumed to be necessarily indicative of hemoglobinuria, because red urine may also be produced by intact red cells, porphyrin, or myoglobin. Microscopic and spectroscopic examination of the urine will reveal the cause of the abnormal color. More often, blood destruction is less rapid and hemoglobinemia and hemoglobinuria are not found.

The fecal urobilinogen may be increased when the urine urobilinogen and the bilirubin in the blood are not significantly greater than normal. The determination of fecal urobilinogen can be accepted as satisfactory for the purpose of diagnosis unliss antibiotics affecting the bacterial flora of the intestine have been withheld for at least 20 days prior to the start of collection of feces.

The anemia may be mild or severe. It is usually normocytic, but may be macrocytic, especially during the stage of rapid regeneration when many relatively immature and reticulated cells are present. Values for hemoglobin and red blood cell counts are depressed to an equal degree; as a general rule, because the iron liberated in the hemolysis of the red blood cells is used all over again, an iron deficiency type of anemia does not develop.

In the stained blood smear the red blood cells may be normocytic or macrocytic, but except in Thalassemia, they are seldom hypochronic; polychromatophilia and reticulocytosis are usually present in the blood smear, and nucleated red blood cells are not unusual.

Howell-Jolly bodies may be present; there may be marked anisocytosis, but there is usually slight poikilocytosis, except in patients with sickle-cell anemia and in severe hemolytic syndromes where there may be much poikilocytosis. Spherocytes may be numerous: spherocytosis is most common in hereditary spherocytosis, but cannot be relied on to differentiate between congenital and acquired types.

The macroytosis may be confused with that of P.A., but the reticulocytosis and regenerative polychromasia are not usual in this disease.

The leukocyte counts are usually normal, but may be elevated or may be low. There may be a "shift to the left". Occasionally

TABLE XII. ROUTINE LAB FINDINGS IN COMMON HEMOGLOBINOPATHIES AND IN THALASSEMIA

Diagnosis	Hemoglobin GMS %	M.C.H.C.	M.C.V.	Reticulocytes	Peripheral Smear	Sickling Test	Fetal Hemoglobin %	Electrophoresis Paper	Electrophoresis Starch: % A_2
Sickle Cell Trait	N.	N.	N.	N.	N.	+	<2	A+S	N.
Sickle Cell Anemia	6-8	N.	N.	I.	‡ *	+	1-15	S	Not Detectable
Hemoglobin C Trait	N.	N.	N.	N.	* *	—	<2	A+C	Not Detectable
Hemoglobin C Disease	N. or D.	N.	N.	N. or I.	* * * *	—	1-10	C	None
Hemoglobin C+S Disease	Usually D; occasionally N.	N.	N.	I.	† * *	+	1-5	C+S	None
Thalassemia Minima Including Hypochromic R.B.C.	11-15.5 RBC 4-7 Mill.	N. or D.	N. or D.	N.	* o Rare	—	N. to >2	A	I.
Thalessemia Minor	9-11	D.	D.	Usually N.	* o	—	N. to >2	A	I.
Thalassemia Intermedia	6-9	D.	D.	I.	* * □ o	—	I.	A	I.
Thalassemia Major	3-6	D.	D.	I.	‡ * □ o	—	Usually >5	A (F)	I.
Hemoglobin S—Thalassemia Disease	Usually D; may be N.	Usually D; may be N.	Usually D; may be N.	Usually I.	† * o	+	2-24	S. or S+A (F)	Not Detectable
Hemoglobin C—Thalassemia Disease	Usually D; may be N.	Usually D; may be N.	Usually D; may be N.	Usually I.	* * o •	—	2-15	C. or C+A (F)	Not Detectable

N.=Normal D.=Decreased I.=Increased •=Spherocyte □=Hypochromic Macrocyte
†=Sickle Cell *=Target Cell o=Hypochromia +=Positive ‡=Nucleated R.B.C.
—=Negative

myelocytes and even rare myecloblasts be present.

The number of the platelets is usually normal but may be elevated or depressed.

The nomenclature of antibodies is rather confusing. Some definitions of antibodies follow:

agglutinins are antibodies which cause agglutination of red blood cells. The antigen of the r.b.c. is called an agglutination.

hemolysins are antibodies which cause hemalysis of red blood cells in the presence of complement.

autoantibodies are antibodies which are capable of acting on the patient's own red blood cells.

isoantibodies are antibodies which are capable of acting on the red blood cells from normal subjects. Isoantibodies may be "nonspecific", i.e., they act on red blood cells independently of their blood group. They may be "specific", i.e., they act only on red blood cells of a certain blood group.

"*complete*" antibodies are antibodies which are capable of causing agglutination or hemolysis in the presence of saline.

"*incomplete*" antibodies can be detected in 4 ways: by the antiglobulin (Coombs') test, by means of trypsinized r.b.c. by titration in an albumin medium rather than a saline media, and by titration in the presence of large antisomatic molecules.

In general, hemolytic anemias are divided into two groups

A. Hemolytic anemias due to intracorpuscular causes and
B. Hemolytic anemias due to extracorpuscular causes.

In the *intracorpuscular hemolytic anemias* the defect resides within the red blood cells. The hemolytic anemias due to an intracorpuscular defect are all inherited disorders. With the possible exception of paroxysmal norturnal hemoglobinuria. Therefore, in this group a careful history of the presence of anemia, jaundice, and splenomegaly in relatives is of great importance. However, either a positive or a negative history may be very misleading and it is by far better to examine all available relatives: do CBC, serum bilirubin, stool and urine urobilinogen.

In general, antibodies are absent from the blood of patients with hereditary hemolytic anemia (intracorpuscular).

The diagnostic tests of value in the differentiation of the intracorpuscular hemolytic anemia are listed in Table XII and Table XIII.

TABLE XIII. SPECIAL DIAGNOSTIC FEATURES OF THE INTRACORPUSCULAR HEMOLYTIC ANEMIAS

Condition	R. B. Cells Morphology	Increased Osmotic Fragility	Acid Serum	Abnormal Hemoglobin Electrophoresis
Hereditary Spherocitosis	Spherocytes[1]	+	O	O
Hereditary Nonspherocytic Anemia	Normocytes	O	O	O
Hereditary Elliptocytosis	Elliptocytes	O	O	O
Paroxysmal Nocturnal Hemoglobinuria	Normocytes	O	+	O
Hereditary Hemoglobinopathies	Variable[2]	O[3]	O	+

[1]Spherocytes are not pathognomonic of hereditary spherocytosis. They may also be increased in some pts with acquired hemolytic anemia.

[2]See Table.

[3]In the presence of target cells the osmotic fragility will be decreased.

Editorials

IS THERE A NEED?

ANDREW M. GEHRET, M.D.

I swear by Apollo the physician, by Aesculapius, Hygeia and Panacea, and I take to witness all the gods, all the goddesses, to keep, according to my ability and my judgment, the following Oath:

"To consider dear to me as my parents, him who taught me this art; to live in common with him, and, if necessary, to share my goods with him; to look upon his children as my own brothers, to teach them this art, if they so desire, without fee or written promise; to impart to my sons and the sons of the master who taught me and the disciples who have enrolled themselves and have agreed to the rules of the profession, but to these alone, the precepts and the instruction. . . "

All of us will recognize the above, as the first portion of the Hippocratic Oath, administered to us as fledgling physicians.

Recently a respected senior physician of our state, a member of the Medical Society of Delaware, at a public meeting, requested the founding of a College of Medicine in Delaware. Our state, of course, is on the eastern sea-board with medical centers, New York, Philadelphia and Baltimore, within easy reach. Who would benefit from such an undertaking, and, IS THERE A NEED?

The prime objective of any institution dedicated to the care of the sick, be it hospital, College of Medicine, or any of the ancillary organizations, is the welfare of the patient.

To any member of the teaching staff of a College of Medicine, the greatest stimulus to his constant search for advanced knowledge is the presence, at his feet, of keen young intellects thirsting for instruction.

To other practicing physicians of the community and the state, the mere presence of a fountain-head of knowledge, within easy reach, would act as a goad to greater endeavor with the resultant elevation of the status of care for those who seek help for their infirmities.

Despite the large list of June medical graduates each year, the number of hospital internships available renders it impossible for all of these positions to be filled, and, as a result, medical care, of necessity, must be down-graded. In our own state, very few of our extremely small number of hospitals achieve their quota of Grade-A Medical School graduates to fill house staff positions. As a result, by necessity, rather than by choice, hospital authorities must fall back on the foreign trained to round out their hospital personnel. In addition to a frequent, very serious, handicap of language difficulty, some of the Colleges of Medicine in foreign lands do not approach the stature of those in the United States.

Several near-by medical centers have discontinued the position of intern in their own hospitals. Whether this is altruism or failure to achieve their quota, the writer knoweth not. These same institutions are achieving a continued high level care of all their patients by the use of Junior and

Senior medical students on the wards and in the private rooms. Under close observation and supervision, these students receive earlier and closer contact with the patient, rather than being subjected to the old, dry, stilted and frequently soporific lecture method.

Is there a need for a College of Medicine in the State of Delaware?

Medical schools do not fling open their doors for the prospective students within ten minutes or a month or a year after the germination of the idea. A recent estimation of population trend placed the number of citizens of this state at the figure, 600,000 by the year 1970. That is but ten short years. This figure, 600,000, does not include the immediate and surrounding portion of the Pen-Jer-Del territory.

While the preponderance of physicians in this state is located in the northern part of New Castle County, specifically Wilmington, there is a distinct need for greater care in the burgeoning suburbs. In the southern portions of the state, physicians are few and far between. Laymen are constantly imploring the Medical Council and the State Board of Medical Examiners: "Please send us a doctor." There are just not enough capable physicians available. As a result, the fringe groups are moving in as barnacles on the under-side of the hull of Medicine.

Is there no need for a College of Medicine in the State of Delaware?

Do the physicians of Delaware have a challenging duty, greater than their appointed daily round of patients?

Books

Recent Accessions to the Library of The Academy of Medicine

ALLERGY

Jamar, J. M.: International Textbook of Allergy, 1959. Thomas

ANATOMY

Miroyiannis, Stanley D.: 501 Questions and Answers in Anatomy, 1959. Vantage Press

ANESTHESIOLOGY

Lee, J. Alfred: A Synopsis of Anaesthesia, 4th ed., 1959. Williams and Wilks

BACTERIOLOGY

Gale, E. F.: Synthesis and Organization in the Bacterial Cell, 1959. John Wiley & Sons

Schaub, Isabelle G.; Foley, M. Kathleen; Scott, Elvyn G.; and Bailey, W. Robert: Diagnostic Bacteriology, 5th ed., 1958. Mosby

CARDIOVASCULAR SYSTEM

Boyles, Paul W.: Antithrombotic Therapy, 1959. Grune and Stratton

CLINICAL PATHOLOGY

Hoeprich, Paul D. and *Ward, John R.*: The Fluids of Parenteral Body Cavities, 1959. Grune and Stratton

Levinson, Samuel A. and *MacFate, Robert P.*: Clinical Laboratory Diagnosis, 5th ed., 1956. Lea and Febiger

ENDOCRINOLOGY

Simpson, S. Leonard: Major Endocrine Disorders, 3rd ed., 1959. Oxford University Press

HISTORY OF MEDICINE

Gordon, Benjamin Lee: Medieval and Renaissance Medicine, 1959. Philosophical Library

Rowntree, Leonard G.: Amid Masters of Twentieth Century Medicine, 1958. Charles C. Thomas

IMMUNOLOGY

Burnet, Sir MacFarlane: The Clonal Selection Theory of Acquired Immunity, 1959. Vanderbilt University Press

MISCELLANEOUS

Jordan, Edwin P.: The Physician and Group Practice, 1958. Year Book

NEOPLASTIC DISEASES

Bluefarb, Samuel M.: Cutaneus Manifestations of the Malignant Lymphomas, 1959. Thomas

Frantz, Virginia Kneeland: Tumors of the Pancreas, 1959. Armed Forces Institute of Pathology

Nettleship, Anderson: Basic Principles of Cancer Practice, 1952. Williams and Wilks

Steward, Harold L.; Snell, Katherine C.; Dunham, Lucia J. and *Schlyen, Samuel M.*: Transplantable and Transmissible Tumors of Animals, 1959. Armed Forces Institute of Pathology

NEUROLOGY

Gibbs, Frederic A. and *Stamps, Frederick W.*: Epilepsy Handbook, 1958. Thomas

In Brief

And Delaware?

New York, Pennsylvania, California, Ohio, Illinois and Texas have contributed 41% of all first year medical students in 1957-58. Of the 84 medical schools in this country, one of the oldest is the University of Pennsylvania School of Medicine (1765); the newest is Albert Einstein College of Medicine which graduated its first class in June, 1959.

Dr. Robert C. Anderson, director of the Southern Regional Education Board, pointed out that of the 16 states of the Southern Regional Education Compact, only one—Delaware—is without a medical school or the prospect of one.

Did You Know?

Russia has a standing order for several — 6 to 8 — copies of all medical books published in the U.S.A.

Medical Author

The manuscript of a new book by Arthur J. Heather, M.D., medical director of the Department of Physical Medicine and Rehabilitation of the Eugene du Pont Memorial Hospital, Wilmington, has been accepted by MacMillan for publication and is now in galley form. Dr. Heather's book is a manual for the care of the severely disabled patient and is pointed at both the nursing and medical professions.

National Foundation Fellowships

Fellowships for the clinical study of arthritis and related diseases are now being made available by the National Foundation, 800 Second Avenue, New York City. Only licensed citizens are eligible. Applications must be received by: Feb. 1, for consideration, May 1, 1960; Aug. 1, for consideration, Nov. 1, 1960; Nov. 1, for consideration, Feb. 1, 1961. Health Scholarships in nursing, occupational therapy, medical social work and medicine are also being offered. Credentials and applications for 1960 must be mailed to the same address by April 1, 1960.

Hospitals Elect New Officers

At St. Francis Hospital, Richard C. Hayden, M.D., president; Joseph F. Hughes, M.D., president-elect; Peter J. Olivere, M.D., secretary and Frank J. Gilday, M.D., treasurer.

At Wilmington General Hospital, Leslie W. Whitney, M.D., president;; Philip D. Gordy, M.D., vice-president; Thomas J. Miller, M.D., secretary and Joseph V. Casella, M.D., treasurer.

Beebe Hospital Expansion Plans

Ground was broken for the new nurses' school and residence addition to Beebe Hospital, Lewes, Delaware, which will be completed by next summer. In addition to financing this, it is expected that the $850,000 campaign will also serve to build a new hospital wing and modernize existing hospital facilities within the next few months.

Item

Dr. S. S. Bjornson, formerly medical examiner for Delaware is now assistant pathologist at the Wilmington General Hospital.

Chest X-ray Milestone

Dr. Lawrence Phillips, diagnostician for Delaware's Anti-Tuberculosis Society and retired medical director of Emily P. Bissell Hospital, has been serving Delawareans by reading chest x-rays since he first offered his services to the Society in 1942. Recently he passed his 500,000th reading and is well on his way into the second half million. Dr. Phillips has had a long career as an anti-TB leader and is the man responsible for chest clinics in this state.

Six New Members

The Medical Society of Delaware and the New Castle County Medical Society announce the following members added to the roster: Robert Marion Marine, M.D., a specialist in radiology; Jefferson Medical College '53; office: Delaware Hospital.

Howard A. Lovett, Jr., M.D., general practice; Temple University '54; office: 904 Wilson Road, Wilmington.

Richard H. Weiss, M.D., anesthesiology; Washington University, St. Louis, Mo., '53; office: Wilmington General Hospital.

Jerome J. Bredall, M.D., industrial medicine; St. Louis School of Medicine, '32; office: Chrysler Corp., Newark, Delaware.

William F. Rath, M.D., ophthalmology; Hahnemann Medical '54; office: Professional Building, Wilmington.

Psychiatric Notes

Dr. Fritz A. Freyhan, clinical director and director of research at Delaware State Hospital, has been made editor-in-chief of "Comprehensive Psychiatry," published by Grune and Stratton, Inc., New York City. Dr. Kurt Anstreicher, acting assistant clinical director of the hospital, will be assistant editor. Dr. Freyhan was recently interviewed by Dave Garroway on the "Today" show during which he took part in a panel discussion on schizophrenia.

Dr. M. A. Tarumianz, Superintendent of the Delaware State Hospital has ended his term as chairman of the Northeast State Government Conference on Mental Health.

A special ten-bed ward for psychotic children has been opened at the Governor Bacon Health Center where the intensive care of a medical staff will lessen their chances of remaining life-long patients.

Dr. Albert L. Ingram, Jr., of Wilmington represented Delaware at the South's first regional conference sponsored by the Southern Regional Education Board's mental health training and research program, in Atlanta. Dr. Ingram spoke in Wilmington recently on the "Family and Delinquency."

Fire Alarm

The National Fire Protection Association charges hospitals with a moral responsibility to meet minimum fire safety hazards in operating rooms. It has been demonstrated that the most commonly used anesthetics are also the most flammable ones.

Noteable

Talleyville, Delaware has 60 members in its Fire Company who have received full Red Cross certification for completing courses in advance first aid. Joseph Glick, M.D., taught the volunteer members first aid for bone, joint and muscle injuries.

DEDICATORY REMARKS

Delivered at the Dedication of the Delaware Academy of Medicine

I feel deeply honored that you have asked me to take part in this dedication of your new Academy of Medicine building — truly a physical and professional monument to the physicians and dentists of Delaware.

Invariably I feel a surge of pride in the magnificent achievements of American medicine whenever I see a building such as this. Not only will it serve as a physical facility, but even more important, I believe, it stands as a tangible representation of a spirit that is responsible for the great progress in the art and science of medicine.

In words of rare insight, the English philosopher Hobbes once observed:

"Felicity consists in *prospering, not* in *having* prospered."

This thought offers a strong impetus for continual striving — and prospering. When we lay down our tools, sit back on the job or throw up our hands in despair or resignation, then our felicity, as well as our progress, comes to a halt.

But such achievements as this fine new building are an encouraging reminder that the physicians and dentists of America are not content to stand still, to rest on their laurels.

No, we are continually working to improve our knowledge, to acquire new ideas to conquer disease and to raise the health of the nation to the highest possible level.

Medicine may never wipe out all disease and suffering. However, we can certainly reduce the potency and curtail the deadliness.

The universality of pain and suffering are sufficient challenges for our unhesitating efforts in the direction of protection. And the sublime joy only a doctor can experience when he relieves misery or restores health to the ailing — this is the highest reward we can ask.

No, I have no fears for the future of medical progress, so long as there are dedicated men and women such as you of the Medical and Dental Societies of Delaware. And so long as medicine continues to forge ahead, with buildings such as this, we can all be proud of our efforts.

In behalf of the American Medical Association, I extend warmest congratulations to the physicians and dentists of Delaware for this splendid achievement.

Your medical society is one of the very oldest in the nation, and you have shown your fellow organizations that the Medical Society of Delaware continues to be among the leaders of American medicine.

Louis M. Orr, M.D.
President, American Medical Association

Wilmington, Delaware
Wednesday Evening, October 14, 1959

Auxiliary Affairs

PRESIDENT'S MESSAGE

Woman's Auxiliary to the New Castle County Medical Society

A SUCCESSFUL AUXILIARY

We can do a marvelous job if we women do nothing more than know each other — have faith in our organization and in each other.

WE CAN ACCOMPLISH THIS IF WE:

Contact anyone of the chairmen below and join in the activities of our Auxiliary by working on any committee.

Never miss a meeting — there are only five in an Auxiliary year.

Bring a member who might not have come — or a potential member.

Patronize the Annual Dance.

Volunteer our services for and attend the Bridge and Fashion Show.

Subscribe to the Bulletin — only $1.00.

Read the A.M.A. News — *Be Informed.*

Our husbands are in need of good public relations . . . let us be their agents.

Mrs. Joseph J. Davolos, President

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DATES TO REMEMBER

January 26, 1960	Executive Board Meeting, Academy of Medicine	9:30 A.M.
	Regular Meeting	11:30 A.M.
	(Bring green stamps to obtain prizes for Bridge Party)	
February 6, 1960	Dance — Academy of Medicine	6:00 P.M.
March 17, 1960	Bridge and Fashion Show, DuPont Country Club	12:30 P.M.
March 29, 1960	Executive Board Meeting, Academy of Medicine	9:30 A.M.
	Regular Meeting	11:30 A.M.
May 24, 1960	Executive Board Meeting, Academy of Medicine	9:30 A.M.
	Regular Meeting	11:30 A.M.

MAJOR MEDICAL MEETINGS IN DELAWARE

Standing Schedule

Beebe Hospital	General Staff	2nd Friday	Monthly
Delaware Hospital	General Staff	2nd Tuesday	Feb., May, Sept., Dec.
Kent General Hospital	General Staff	3rd Tuesday	Monthly
Memorial Hospital (Wilmington)	General Staff	2nd Tuesday	Jan., March, June, Oct.
Milford Memorial Hospital	General Staff	2nd and last Tuesdays	Monthly
Nanticoke Memorial Hospital	General Staff	1st Thursday	Monthly
St. Francis Hospital	General Staff	4th Tuesday 1st Tuesday	March, May, Oct. December
Wilmington General Hospital	General Staff	4th Tuesday	Jan., April, Sept., Nov.

Kent County Medical Society	Monthly Meeting	3rd Tuesday	September - June
New Castle County Medical Society	Monthly Meeting	3rd Tuesday	September - June
Sussex County Medical Society	Monthly Meeting	2nd Thursday	September - June

Delaware Academy of General Practice	Monthly Meeting	1st Tuesday	September - June
Delaware Pathology Society	Weekly Meeting	Each Friday	

Special Schedule

Delaware Heart Association	Board of Directors Meeting	Dover, Delaware Speaker: Charles K. King, M.D.	January 21, 1960
Delaware Academy of Medicine	Annual Meeting	Wilmington, Delaware	February 3, 1960 4:30 P.M.
Medical Society of Delaware	Annual Meeting	Rehoboth, Delaware	September, 1960

LECTURE COURSE

Subject: Basic Electrocardiography

Schedule: Part I

Time — Every Thursday afternoon 4-5 p.m.
Dates: From October 29, 1959 through February 25, 1960

Place: Memorial Hospital, Wilmington

Schedule: Part II

Time — Same as for Part I
Dates: March 3rd through March 31st, 1960
Arrangements must be made for Part II only.

For full details regarding this series write to the Director of Medical Education, Memorial Hospital, Wilmington

TWO-WAY RADIO CONFERENCES FOR THE COMING MONTH

Sponsorship: *Medical Society of Delaware, Pennsylvania Hospital, Smith Kline & French Laboratories.*

Date *Topic and Faculty*

Jan. 26 — "Value of Preventive Measures in Atherosclerosis." Peter T. Kuo, M.D., Assistant Prof. Medicine, University of Penna. School of Medicine.

Feb. 2 — "Role of Steroids in Rheumatoid Arthritis." Richard T. Smith, M.D., Director, Department of Rheumatology; Physician to Pennsylvania Hospital.

Feb. 9 — "Laboratory Workup of the Patient with Jaundice." Alexander Rush, M.D.

Feb. 16 — "Carcinoma of the Cervix." Robert A. Kimbrough, M.D., Director, Division of Obstetrics and Gynecology, Penna. Hospital.

Underweight Children Gain and Retain Weight with Nilevar®

One of the most convincing evidences of the anabolic activity of Nilevar, brand of norethandrolone, has been its ability to improve appetite and increase weight in poorly nourished, underweight children.

A highly important feature of the weight gain thus produced is that it is not ordinarily manifested by deposition of fat but as muscle tissue resulting from the protein anabolism induced by Nilevar.

Anorexia and "Weight Lag" Study—Brown, Libo and Nussbaum have reported* consistent and definite increases in rate of weight gain in eighty-six patients, ranging in age from 7 weeks to 15½ years. This beneficial action of Nilevar was observed in the patients with organic and traumatic disorders as well as those whose only complaints were poor appetite and/or persistent failure to gain weight.

In this study, the weight gained was not lost after discontinuance of Nilevar therapy although many patients did not continue the sharp gains effected by the drug.

The authors are of the opinion that Nilevar is a highly useful anabolic agent for influencing weight gain in underweight children.

When Nilevar is administered to children a dose of 0.25 mg. per pound of body weight is recommended and continuous dosage for more than three months is not recommended.

Nilevar is supplied as tablets of 10 mg., drops of 0.25 mg. per drop and ampuls of 25 mg. in 1 cc. of sesame oil. Further dosage information in Searle Reference Manual No. 4.

G. D. Searle & Co., Chicago 80, Illinois.
Research in the Service of Medicine.

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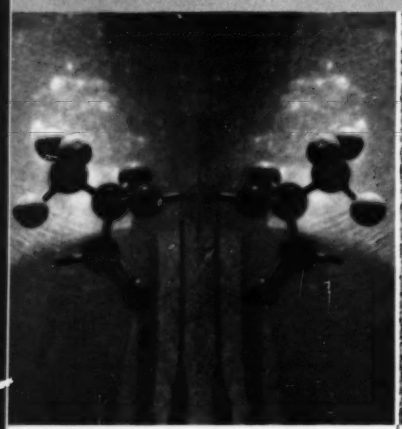
*Brown, S. S.; Libo, H. W., and Nussbaum, A. H.: Norethandrolone in the Successful Management of Anorexia and "Weight Lag" in Children, Scientific Exhibit presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 20-23, 1958.

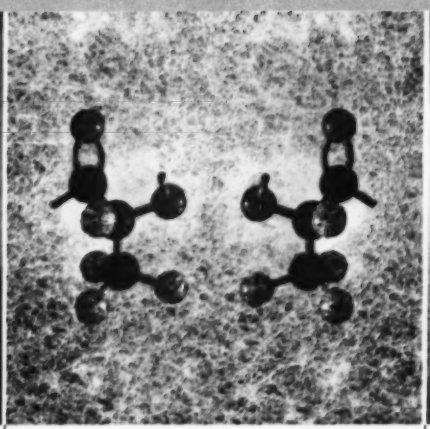
AN ANNOUNCEMENT
OF IMPORTANCE
FROM
BRISTOL LABORATORIES

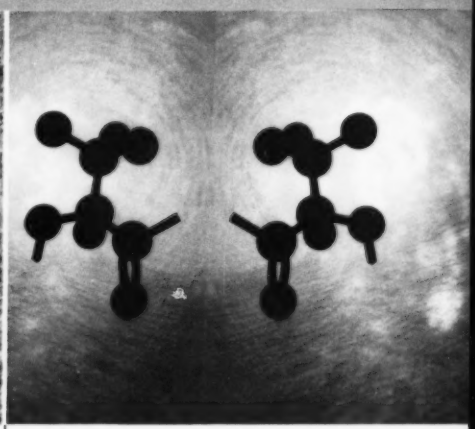
The first synthetic penicillin available for general clinical use

MAJOR THERAPEUTIC

SYNC







BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V

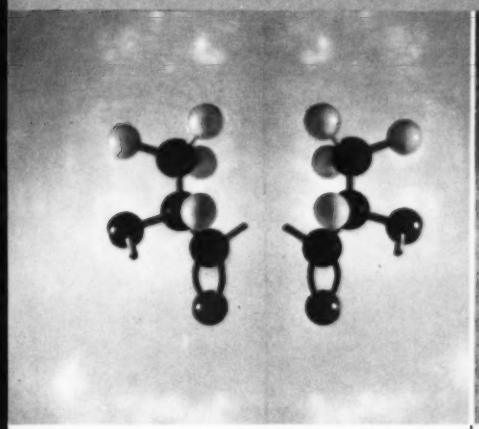
SAFER ORAL ROUTE PROVIDES HIGHER BLOOD LEVELS THAN INTRAMUSCULAR PENICILLIN G

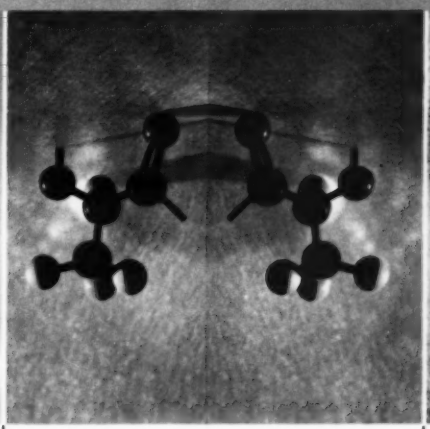
IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

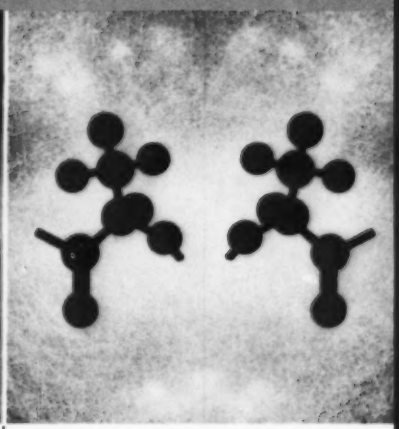
ADVANTAGES ACCOMPANY MOLECULAR ASYMMETRY

ILLIN™

POTASSIUM PENICILLIN-152







ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSE

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN

BRISTOL

ORIGIN OF A NEW SYNTHETIC PENICILLIN

In March, 1957, Dr. John C. Sheehan of the Massachusetts Institute of Technology announced the total synthesis of penicillin from common raw materials, thus solving a problem which had baffled research workers for more than 15 years. Although total synthesis was not commercially practicable, this work, sponsored by Bristol Laboratories, made possible the subsequent synthesis of new penicillins not occurring in nature. Later scientists at Beecham Laboratories in England discovered that a key intermediate (6-aminopenicillanic acid) could be produced by a fermentation process. With these achievements, large scale production of synthetic penicillins became feasible.

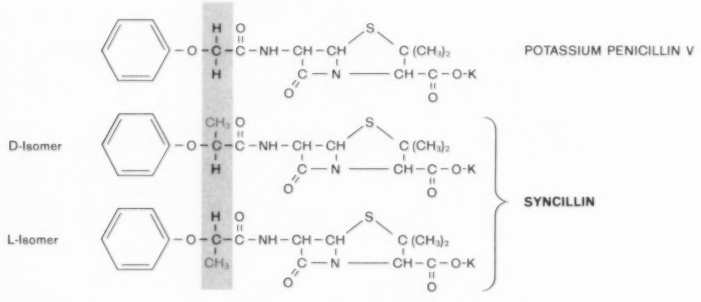
Organic chemists at Bristol then embarked upon an intensive program to develop better penicillins. Over five hundred were synthesized and underwent preliminary screening. Forty-six showed sufficient promise to warrant further investigation. Extensive microbiological, pharmacological, and clinical screening indicated that one compound, SYNCILLIN, had advantages of major importance over other penicillins.

SYNCILLIN is the N-acylation product of 6-aminopenicillanic acid and α-phenoxypropionic acid (the phenylether of lactic acid). It is freely soluble in water and remarkably resistant to decomposition by acid. The acid stability of SYNCILLIN is equivalent to that of penicillin V at pH 2 and pH 3 at 37° C.[1]

SIGNIFICANCE OF MOLECULAR ASYMMETRY AND ISOMERIC COMPLEMENTARITY

SYNCILLIN has a molecular configuration similar to penicillin V, but contains an additional CH_3 group so positioned as to render the adjacent carbon atom asymmetric. (In the formulae below, the added CH_3 group is shown in blue and the asymmetric carbon atom in red.) As a result, SYNCILLIN occurs as a mixture of two isomers.

Each isomer has been synthesized in essentially pure form and found to possess distinctive chemical and biological properties. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. As produced, SYNCILLIN is a mixture of the L-isomer and the D-isomer. As will be shown later, the antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than either isomer alone against many organisms. This phenomenon is referred to here as *isomeric complementarity*.



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

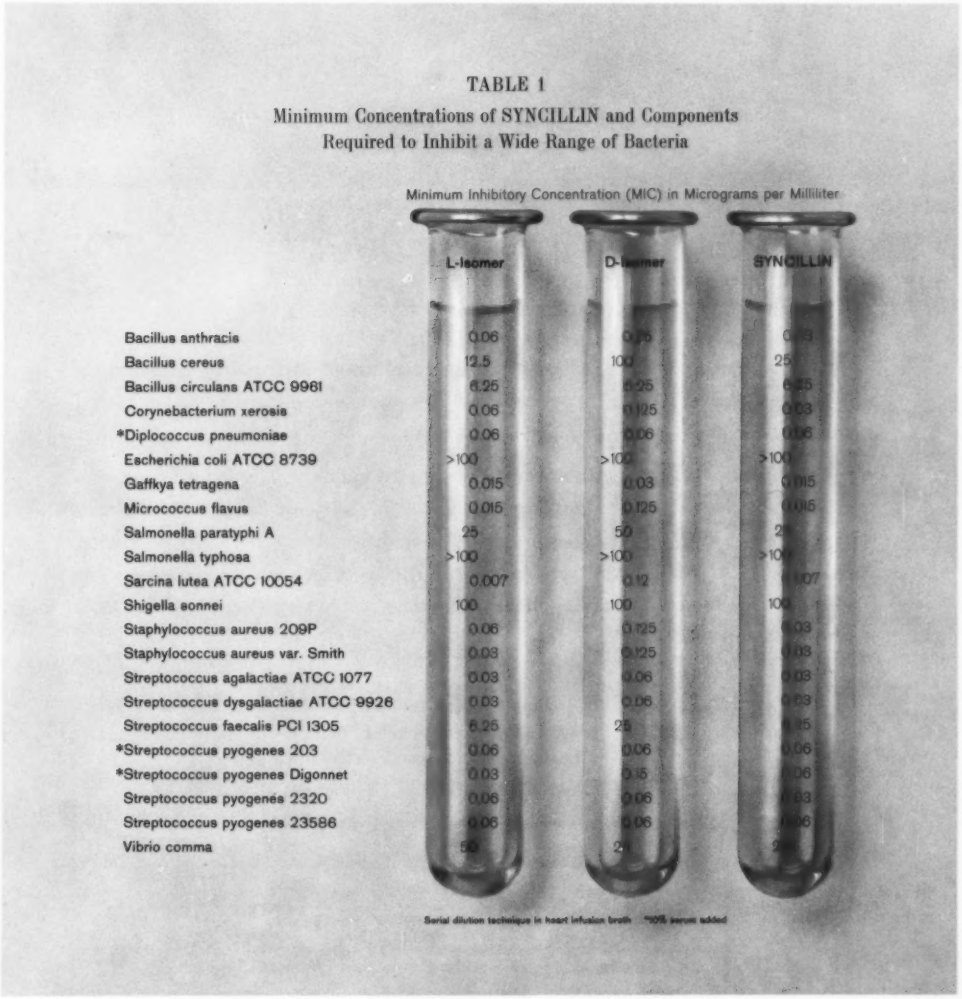
ISOMERIC COMPLEMENTARITY DEMONSTRATED IN VITRO

The *in vitro* minimum inhibitory concentration (MIC) of SYNCILLIN and of each of its two component isomers was determined for a variety of common pathogens and laboratory test organisms. As may be seen from Table 1, all three are highly effective against penicillin-susceptible staphylococci and against pneumococci, streptococci, gonococci, and corynebacteria; all are ineffective against Salmonella, *E. coli*, and other gram-negative coliform bacilli.

SYNCILLIN was more active against many of the test strains including some streptococci and staphylococci than either of its components. This demonstrates *in vitro* the phenomenon of isomeric complementarity.

TABLE 1

Minimum Concentrations of SYNCILLIN and Components Required to Inhibit a Wide Range of Bacteria



SYNCILLIN

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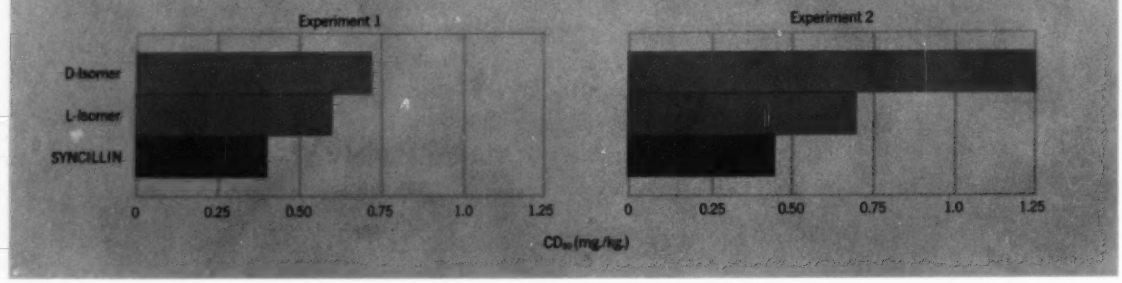
ISOMERIC COMPLEMENTARITY CONFIRMED IN VIVO

To determine the median curative dose (CD_{50}) mice were infected with 100 times the lethal dose of *Staphylococcus aureus*. Each penicillin being tested was administered intramuscularly at the same time, and the dose required to cure half the animals determined. The greater effect of the mixture of the two isomers (SYNCILLIN) is shown in two independent experiments. (See Figure 1.) Note that isomeric complementarity is thus confirmed *in vivo*.

FIGURE 1 — Median Curative Dose (CD_{50}) for *Staphylococcus aureus* (var. Smith) Infections

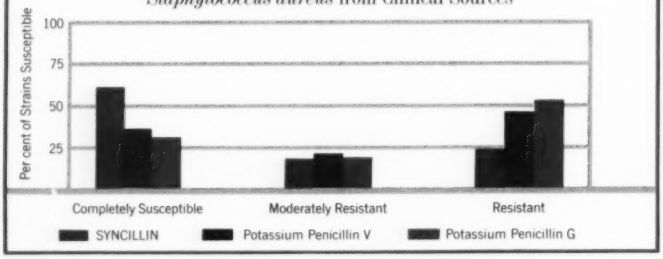


MANY STRAINS OF STAPHYLOCOCCI MORE SENSITIVE TO SYNCILLIN

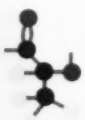
SYNCILLIN has been tested against a large number of strains of *Staphylococcus aureus* isolated from clinical sources. Many organisms resistant to potassium penicillin G and potassium penicillin V proved sensitive to SYNCILLIN.

Wright[2] performed sensitivity studies on 54 strains, the majority of which were resistant or moderately resistant to penicillin V and penicillin G. Thirty-two (60%) of the strains were sensitive to SYNCILLIN, approximately twice as many as with the other penicillins. (See Figure 2.) In two-thirds of the isolates, SYNCILLIN produced inhibition at concentrations lower than those required for either of the other antibiotics. One strain was more sensitive to penicillin G.

FIGURE 2 – *In Vitro* Sensitivity of 54 Strains of Coagulase-Positive *Staphylococcus aureus* from Clinical Sources



Adapted from Wright[2]



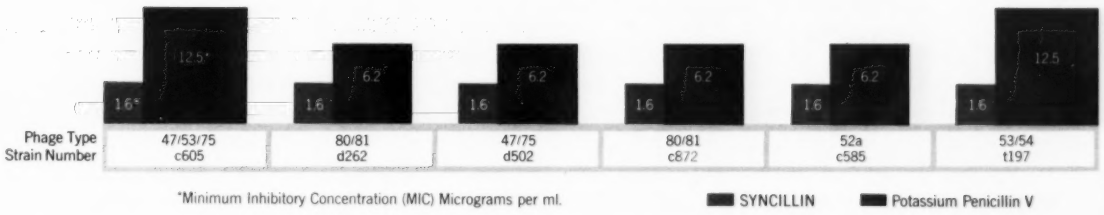
SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Of equal interest are the findings of White.[3] Six penicillin-resistant strains of staphylococci were isolated from hospital infections. None was sensitive to potassium penicillin V. All were sensitive to SYNCILLIN. (See Figure 3.)

FIGURE 3

Minimum Concentrations of SYNCILLIN Required to Inhibit
Hospital Strains of *Staphylococcus aureus* Resistant to Potassium Penicillin V

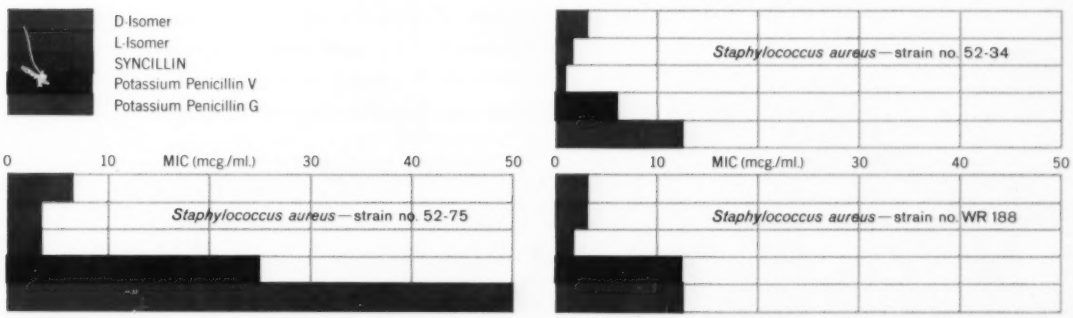


The efficacy of SYNCILLIN against the type 80/81 Staphylococcus (dangerous and widespread in hospitals) is worthy of special attention.

The complementary action of the component isomers is also seen with strains of staphylococci resistant to penicillins. Note that SYNCILLIN is more effective than either isomer against strains 52-34 and WR 188. (See Figure 4.) Against all three strains, SYNCILLIN is effective at concentrations below serum levels, while penicillins V and G are ineffective.

FIGURE 4

Minimum Inhibitory Concentrations (MIC) for Coagulase-Positive
Penicillin-Resistant Strains of *Staphylococcus aureus*



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figure 1)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

SYNCILLIN

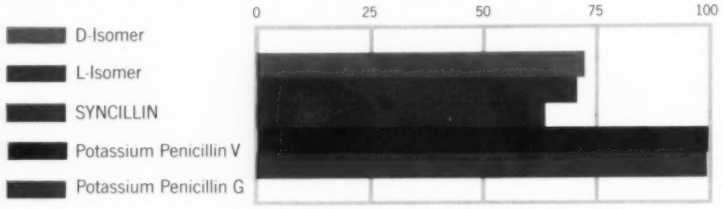
major therapeutic advantages accompany molecular asymmetry

ISOMERIC COMPLEMENTARITY SHOWN BY REDUCED RATE OF INACTIVATION BY PENICILLINASE

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms.[4] As shown in Figure 5, SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers – a further demonstration of isomeric complementarity. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V and penicillin G.

Resistance to SYNCILLIN develops in a slow, step-wise manner characteristic of other penicillins, in contrast to the usually rapid development of resistance to streptomycin.

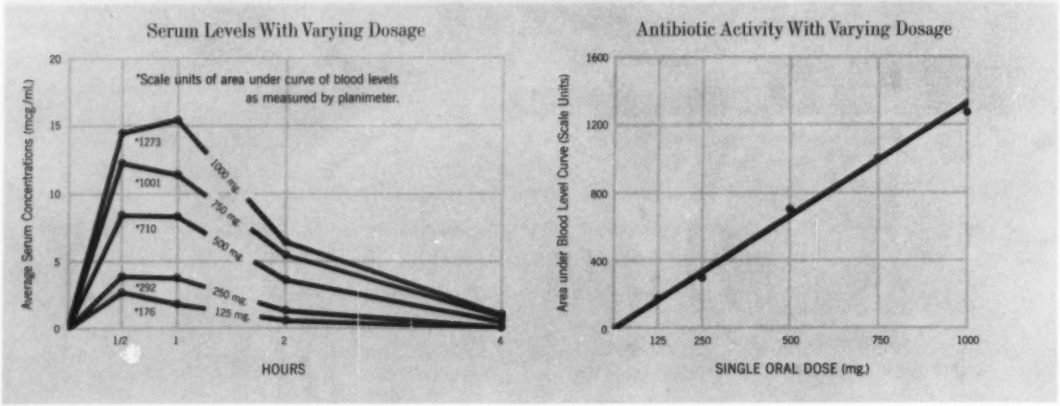
FIGURE 5—Effect of Staphylococcal Penicillinase on Different Penicillins

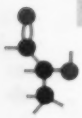


ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSAGE

Cronk[5] studied blood levels after administering varying amounts of SYNCILLIN. (Figure 6.) Total antibiotic activity (obtained by measuring areas under curves with a planimeter) increases rapidly as the dose is doubled. These data show that increased dosage markedly increases serum concentration and thus may enhance the drug's effectiveness.

FIGURE 6





SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

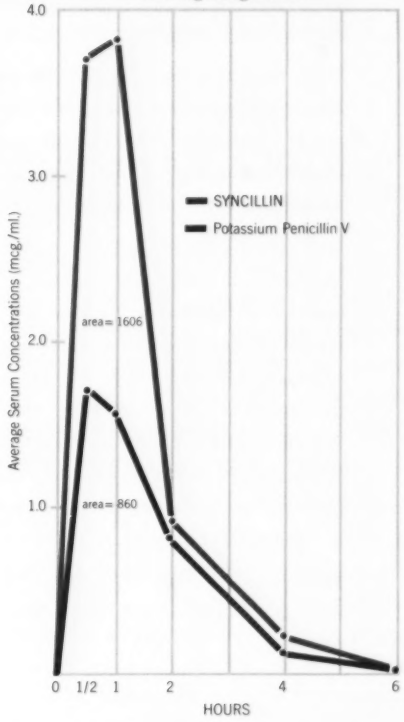
BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V AFTER ORAL ADMINISTRATION

Wright[6] performed comparative crossover blood level studies on volunteer subjects receiving equivalent amounts of potassium penicillin V and SYNCILLIN. The peak concentrations attained during the first hour after administration were twice as high with SYNCILLIN.

The total antibiotic activity as measured by the area under the curves (see Figure 7) indicates an almost 2 to 1 superiority of SYNCILLIN (1606) over potassium penicillin V (860).

The higher blood levels may be of value with organisms of only moderate penicillin-sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition these higher levels may be necessary where there is infection in areas with a poor blood supply.[7] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue.

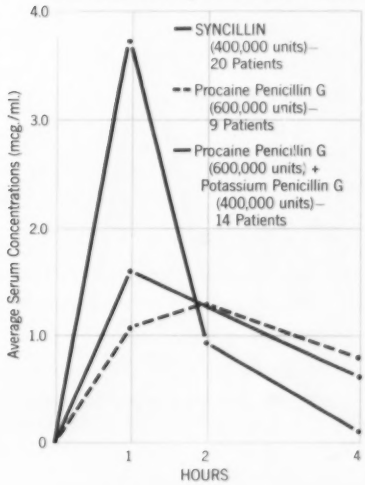
FIGURE 7
20 Subject Crossover
250 mg. Single Dose



BLOOD LEVELS MUCH HIGHER THAN WITH INTRAMUSCULAR PENICILLIN G

In addition, blood levels attained with oral SYNCILLIN[6] are much higher than those with intramuscular penicillin G.[8a, b] (See Figure 8.) Note that the level at one hour for SYNCILLIN (3.8 mcg./ml.) is more than twice as high as with procaine penicillin G, even when reinforced with potassium penicillin G (1.6 mcg./ml.). Since penicillins are *bactericidal,* these intermittent high serum levels can be clinically significant. Thus, SYNCILLIN offers the promise of superior efficacy via the safer oral route.

FIGURE 8—Serum Levels after Oral Administration of SYNCILLIN (250 mg.) and after Intramuscular Injection of Penicillin G



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

SYNCILLIN has been administered in multiple doses to 437 patients and volunteers. One patient developed itching during therapy, possibly an allergic side effect. Another had a purpuric rash, but no relationship to SYNCILLIN was established. No reactions were observed in 9 patients with a known history of sensitivity to penicillin.

While the above data suggests the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *The usual precautions for oral penicillin therapy should be observed.* Patients with histories of asthma, hay fever, urticaria, or previous penicillin-sensitivity should especially be watched carefully. Since SYNCILLIN is administered orally, it may be expected to be safer than parenteral penicillin.

As Flippin[9] recently stated, ". . . it is well established that serious allergy to the drug [penicillin] is most likely to occur following parenteral administration, especially after repeated intramuscular injections; the oral route is least likely to initiate severe hypersensitivity reactions. This can be explained partly by the fact that when reactions develop following oral medication, they are usually slow enough to treat symptomatically; thus the progression of the reaction can usually be interrupted. . . . In view of the relatively high incidence of severe allergy to injectable penicillin, it would seem advisable to employ oral penicillin routinely, except in the control of infections involving the blood stream, endocardium, meninges, etc., in which cases the parenteral route remains the preferred treatment."

SYNCILLIN, like other penicillins, is essentially free of other toxicity. No hematopoietic, hepatic, or renal toxicity was observed in 210 volunteers receiving 1 gm. daily for 2 to 3 weeks.[10]

CLINICAL EFFICACY DEMONSTRATED IN PENICILLIN-SENSITIVE INFECTIONS

Clinical trials conducted by Blau and Kanof,[11] White,[12] Prigot,[13] Robinson,[14] Dube,[15] Ferguson,[16] Rutenburg,[17] Richardson,[18] Bunn,[19] Cronk,[5] Kligman,[10] and Yow [20] demonstrated the efficacy of SYNCILLIN in a variety of streptococcal, staphylococcal, pneumococcal, and gonococcal infections. Conditions treated included respiratory, skin, soft tissue, wound, and chronic urinary tract infections; acute gonorrhea; cellulitis; septicemia; otitis media; gingivitis; and Vincent's angina. In a few patients SYNCILLIN was used for rheumatic fever or gonorrheal prophylaxis.

One hundred seventy-two of one hundred ninety-six patients responded favorably to SYNCILLIN. The failures included 1 patient with pustular dermatoses, 10 elderly patients with chronic urinary tract infections, 1 patient with gonorrhea, 1 patient with a gram-negative infection, and 10 patients with staphylococcal infections. Lack of response of staphylococcal infections was attributed to the presence of resistant organisms or local suppurative foci requiring drainage.

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Relatively few side effects were encountered. One patient experienced moderate itching of the skin which was controlled by an antihistamine. Another reported pruritus ani which did not interfere with therapy. Diarrhea occurred in 4 instances. There was one purpuric rash, but no relationship to SYNCILLIN could be established.

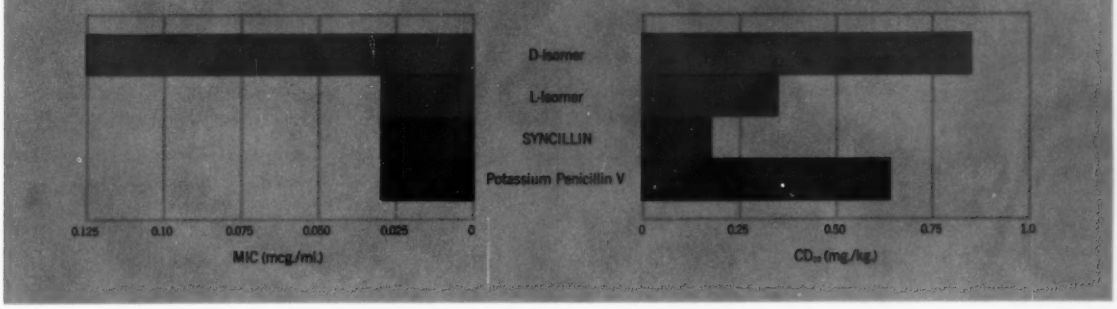
Clinical response usually begins within 24 hours in infections susceptible to SYNCILLIN. Recovery occurs in 4 to 7 days depending upon the severity of the infection. Gonorrheal infections respond very promptly to SYNCILLIN; 500 mg. b.i.d. for two days usually produce bacteriologic cures.

IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

SYNCILLIN is a mixture of isomers. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. Furthermore, the D- and L-isomers have other distinguishing chemical, pharmacological, and microbiological properties. Their *in vivo* and *in vitro* activities differ for many important pathogens. *Against many of the organisms tested, the combination of isome s* (SYNCILLIN) *is much more active than the stronger isomer alone.* This phenomenon of isomeric complementarity is not always demonstrable, for in a few instances SYNCILLIN is slightly less active.

Isomeric complementarity has previously been demonstrated *in vitro* (Figure 4) and *in vivo* (Figure 1). Figure 9 reveals a third form of superiority related to isomeric complementarity. Equal concentrations of SYNCILLIN and penicillin V were required to inhibit this growth of staphylococci *in vitro.* But, *in vivo,* a much smaller amount of SYNCILLIN *(one-third that of penicillin V)* was effective in an experimental infection with the same strain. These observations on complementary action indicated the advantage of producing the mixture of isomers as the medication to be made available for clinical therapy.

FIGURE 9 — Comparison of CD_{50} and MIC Values Against *Staphylococcus aureus* (var. Smith)



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figures 1 and 9)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

— *staphylococcal penicillinase antibiotic inactivation (Figure 5)*

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Indications:

SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins.

SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage:

125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals.

Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

Precautions:

While present data suggest the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *Therefore the usual precautions with oral penicillin therapy must be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, the interval between dosages should be lengthened.

If superinfection occurs during therapy, appropriate measures should be taken.

Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply:

125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

References: 1. Lein, J.: Microbiology report to Bristol Laboratories Inc. 2. Wright, W. W.: Microbiology report to Bristol Laboratories Inc. 3. White, A. C.: Microbiology report to Bristol Laboratories Inc. 4. Dubos, R. J.: Bacterial and Mycotic Infections of Man, 3rd edition, Philadelphia, J. B. Lippincott Co., p. 690. 5. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 6. Wright, W. W.: Clinical report to Bristol Laboratories Inc. 7. Kass, E. H.: Am. J. Med. *18*:764 (May) 1955. 8a. White, A. C.; Couch, R. A.; Foster, F.; Calloway, J.; Hunter, W., and Knight, V.: in Welch, H. and Marti-Ibañez, F.: Antibiotics Annual — 1955-1956, Medical Encyclopedia, Inc., New York, 1956, p. 490. b. Data on file — at Bristol Laboratories. 9. Flippin, H. F.: Pennsylvania M. J. *62*:864 (June) 1959. 10. Kligman, A.: Clinical report to Bristol Laboratories Inc. 11. Blau, S., and Kanof, N.: Clinical report to Bristol Laboratories Inc. 12. White, A. C.: Clinical report to Bristol Laboratories Inc. 13. Prigot, A.: Clinical report to Bristol Laboratories Inc. 14. Robinson, C.: Clinical report to Bristol Laboratories Inc. 15. Dube, A. H.: Clinical report to Bristol Laboratories Inc. 16. Ferguson, B.: Clinical report to Bristol Laboratories Inc. 17. Rutenburg, A. M.: Clinical report to Bristol Laboratories Inc. 18. Richardson, J. H.: Clinical report to Bristol Laboratories Inc. 19. Bunn, P. A.: Clinical report to Bristol Laboratories Inc. 20. Yow, E. M.: Clinical report to Bristol Laboratories Inc.

BRISTOL

major therapeutic advantages accompany molecular asymmetry

SYNCILLIN

to prevent the sequelae of u.r.i. ...and relieve the symptom complex

ACHROCIDIN®

Tetracycline-Antihistamine-Analgesic Compound Lederle

Tonsillitis, otitis, adenitis, sinusitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.[1] To protect and relieve the "cold" patient... ACHROCIDIN.

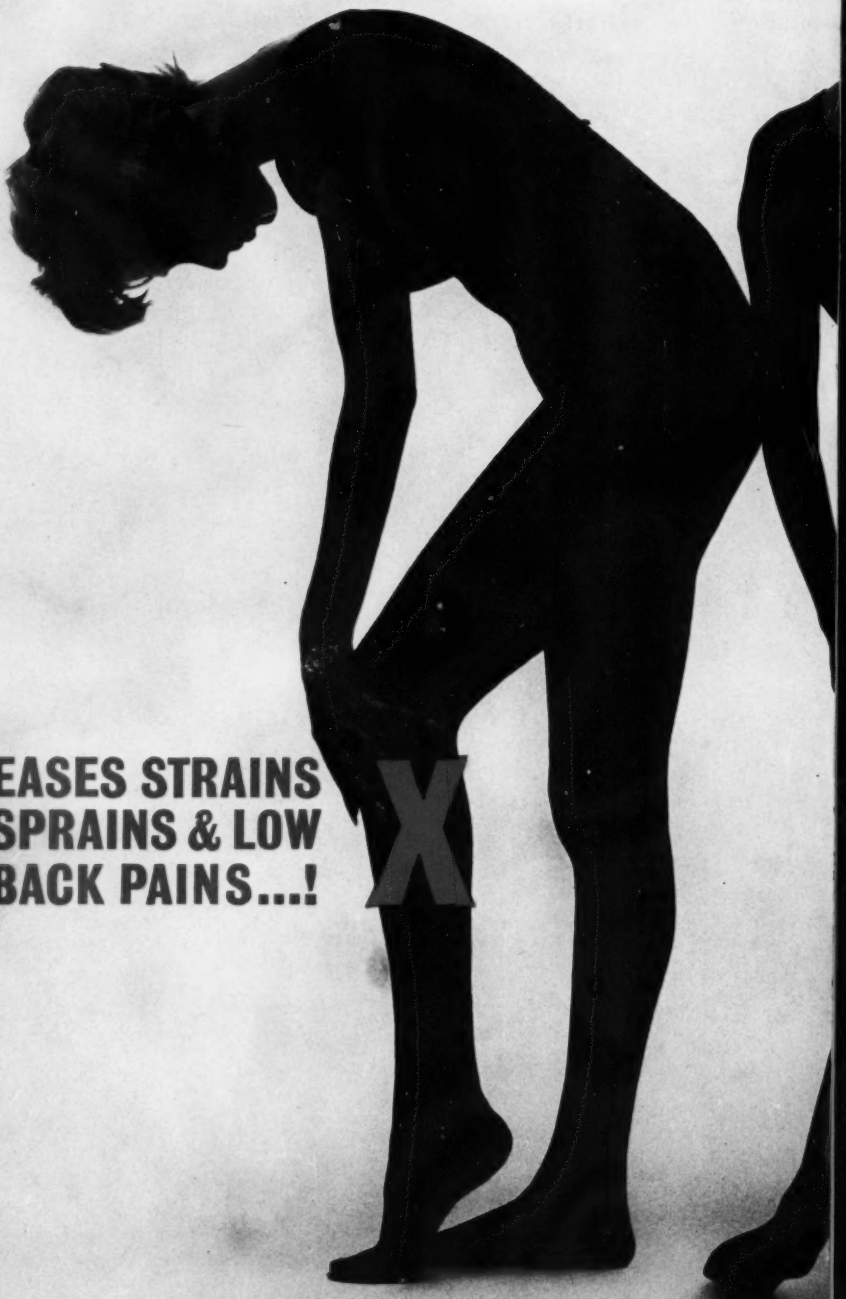
Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP (lemon-lime flavored), caffeine-free.

1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933

Lederle

LEDERLE LABORATORIES,
a Division of
AMERICAN CYANAMID COMPANY,
Pearl River, New York

ANNOUNCING SCHERING'S NEW MYOGESIC[X]



RELA™ **EASES STRAINS SPRAINS & LOW BACK PAINS...!**

CARISOPRODOL

RELA—a new myogesic for better relaxant *and* analgesic therapy—more adept management of spasm and pain in strains, sprains and low back pains.

RELA—though a single drug—is a true myogesic and works rapidly to achieve three desired effects...

Rela relaxes acute muscle spasm
Relief of muscle spasm (96% excellent to good effectiveness)[1]

Rela provides a unique quality of persistent pain relief through its relaxant and analgesic actions
"Relief from pain was usually rapid and sometimes dramatic"[1]

Rela, through relaxation and analgesia, assures daytime ease and nighttime rest
"... A number of patients reported freedom from insomnia which they attributed to freedom from pain."[1]

indications: RELA is most beneficial in those conditions of the musculoskeletal system manifesting pain, stiffness and spasm.

safety: Studies of more than 1400 patients indicate that the toxicity of RELA is exceptionally low. In human subjects, respiratory, blood pressure or blood chemistry changes and/or renal, hepatic or endocrine dysfunction have not been reported.

dosage: The usual adult dosage of RELA is one tablet 3 times daily and at bedtime. RELA has a rapid onset of action, with relief usually apparent within 30 minutes, and persisting for at least 6 hours.

supply: RELA is available as 350 mg., pink, coated tablets in bottles of 30.

1. Kuge, T.: To be published.

H-227

MYOGESIC
muscle-analgesic relaxant

Schering

saturation doses – the hard way!

Each of these food portions contains a saturation dose of one of the water-soluble B vitamins or C. The easy way to provide such quantities of these vitamins with speed, safety and economy is to prescribe Allbee with C. Recommended in pregnancy, deficiency states, digestive dysfunction and convalescence.

In each Allbee with C:		As much as:*
Thiamine mononitrate (B_1)	15 mg.	6.9 lbs. of fried bacon
Riboflavin (B_2)	10 mg.	31½ ozs. of liverwurst
Pyridoxine HCl (B_6)	5 mg.	2 lbs. of yellow corn
Nicotinamide	50 mg.	11 ozs. of roasted peanuts
Calcium pantothenate	10 mg.	¼ lb. of fried beef liver
Ascorbic acid (Vitamin C)	**250 mg.**	¾ lb. of cooked broccoli

*These common foods are among the richest sources of B vitamins and ascorbic acid. H. A. Wooster, Jr., Nutritional Data, 2nd Ed., Pittsburgh, 1954.

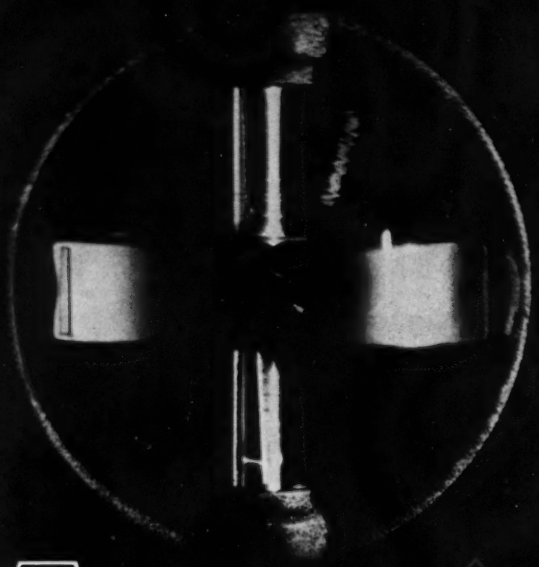
Allbee® with C

Robins

A. H. ROBINS COMPANY, INC.
RICHMOND 20, VIRGINIA

the beauty of these antitussives:

minimal disturbance
of the patient's chemical and psychic balance...



still unsurpassed for total corticosteroid benefits

Aris

Substantiated by published reports of leading clinicians:

- **effective control** of allergic and inflammatory symptoms[1-20]
- **minimal disturbance** of the patient's chemical and psychic balance[1, 4, 5, 8-19]

tocort®

Triamcinolone LEDERLE

At anti-inflammatory and antiallergic levels ARISTOCORT means:

- **freedom from salt and water retention**
- **virtual freedom from potassium depletion**
- **negligible calcium depletion**
- **euphoria and depression rare**
- **no voracious appetite—no excessive weight gain**
- **low incidence of peptic ulcer**
- **low incidence of osteoporosis with compression fracture**

Indications: rheumatoid arthritis; arthritis; respiratory allergies; allergic and inflammatory dermatoses; disseminated lupus erythematosus; nephrotic syndrome; lymphomas and leukemias.
Precautions: With ARISTOCORT all traditional precautions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress symptoms. After patients have been on steroids for prolonged periods, discontinuance must be carried out gradually.
Supplied: Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white). Diacetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

References: 1. Feinberg, S.M., Feinberg, A.R., and Fisherman, E.W.: *J.A.M.A.* 167:58 (May 3) 1958. 2. Epstein, J.I. and Sherwood, H.: *Connecticut Med.* 22:822 (Dec.) 1958. 3. Friedlaender, S. and Friedlaender, A.S.: *Antibiotic Med. & Clin. Ther.* 5:315 (May) 1958. 4. Segal, M.S. and Duvenci, J.: *Bull. Tufts North East M. Center* 4:71 (April-June) 1958. 5. Segal, M.S.: Report to the A.M.A. Council on Drugs, *J.A.M.A.* 169:1063 (March 7) 1958. 6. Sherwood, H. and Cooke, R.A.: *J. Allergy* 28:97 (Mar.) 1958. 7. Duke, C.J. and Oviedo, R.: *Antibiotic Med. & Clin. Ther.* 5:710 (Dec.) 1958. 8. McGavack, T.H.: *Clin. Med.* (June) 1958. 9. Freyberg, R.H.; Berntsen, C.A., and Hellman, L.: *Arthritis and Rheumatism* 1:215 (June) 1958. 10. Hartung, E.F.: *J.A.M.A.* 167:973 (June 21) 1958. 11. Hartung, E.F.: *J. Florida Acad. Gen. Pract.* 8:18, 1958. 12. Zuckner, J.; Ramsey, R.H.; Caciolo, C., and Gantner, G.E.: *Ann. Rheum. Dis.* 17:398 (Dec.) 1958. 13. Appel, B.; Tye, M.J., and Leibsohn, E.: *Antibiotic Med. & Clin. Ther.* 5:716 (Dec.) 1958. 14. Kalz, F.: *Canad. M.A.J.* 79:400 (Sept.) 1958. 15. Mullins, J.F., and Wilson, C.J.: *Texas State J. Med.* 54:648 (Sept.) 1958. 16. Shelley, W.B.; Harun, J.S., and Pillsbury, D.M.: *J.A.M.A.* 167:959 (June 21) 1958. 17. DuBois, E.F.: *J.A.M.A.* 167:1590 (July 26) 1958. 18. McGavack, T.H.; Kao, K.T.; Leake, D.A.; Bauer, H.G., and Berger, H.E.: *Am. J. Med. Sc.* 236:720 (Dec.) 1958. 19. Council on Drugs: *J.A.M.A.* 169:257 (Jan. 17) 1959. 20. Rein, C.R.; Fleischmajer, R., and Rosenthal, A.R.: *J.A.M.A.* 165:1821 (Dec. 7) 1957.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

The clock strikes 2—
and your ulcer patient sleeps undisturbed

ONE 10 MG. DARICON TABLET AT BEDTIME...

controls hypersecretion, hypermotility, and spasm all night long. The sustained anticholinergic efficacy of DARICON is inherent in its structure and does not depend on special coatings.

ONE 10 MG. DARICON TABLET BEFORE BREAKFAST...

provides dependable relief for at least 12 more hours. In a large series of patients with peptic ulcer and other gastrointestinal disorders—some notably refractory to therapy—8 out of 10 responded to DARICON.

DARICON®
oxyphencyclimine hydrochloride

B. I. D. DOSAGE

For 'round-the-clock relief of ulcer and other gastrointestinal disorders

A Professional Information Booklet is available on request from the Medical Department.

Pfizer *Science for the world's well-being™* PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York*

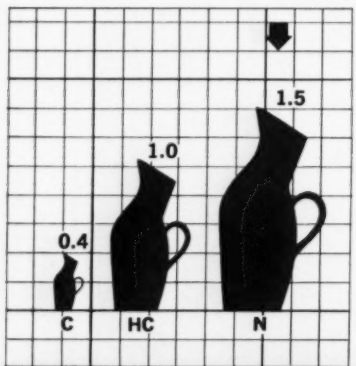
more closely approaches the ideal diuretic

Naturētin

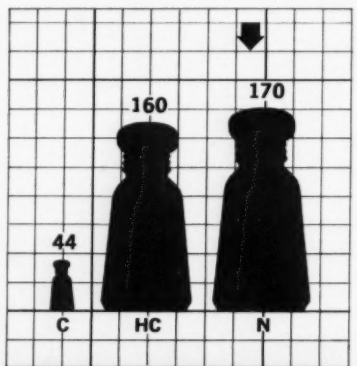
Squibb Benzydroflumethiazide

"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." *Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.*

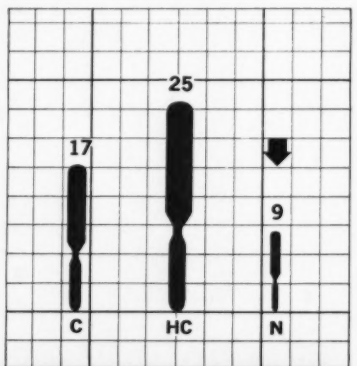
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



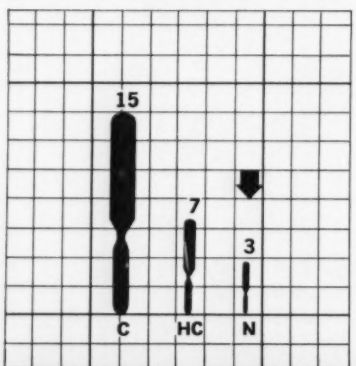
Urinary Volume (liters)
significantly increased
with Naturetin



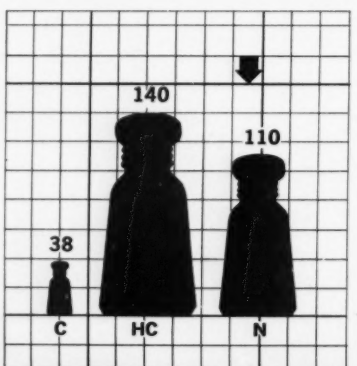
Natriuresis (mEq./24 hr.)
sodium excretion significantly
increased with Naturetin



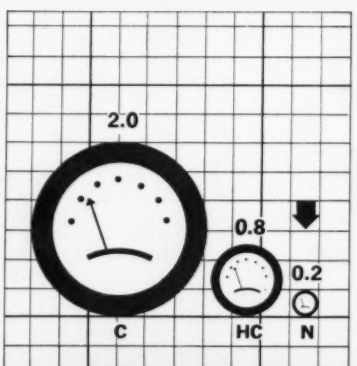
Potassium Excretion
(mEq./24 hr.)
least with Naturetin



Bicarbonate Excretion
(mEq./24 hr.)
least with Naturetin



Chloride Excretion
(mEq./24 hr.)
marked increases



Urinary pH
least increase with Naturetin

Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturētin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturētin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

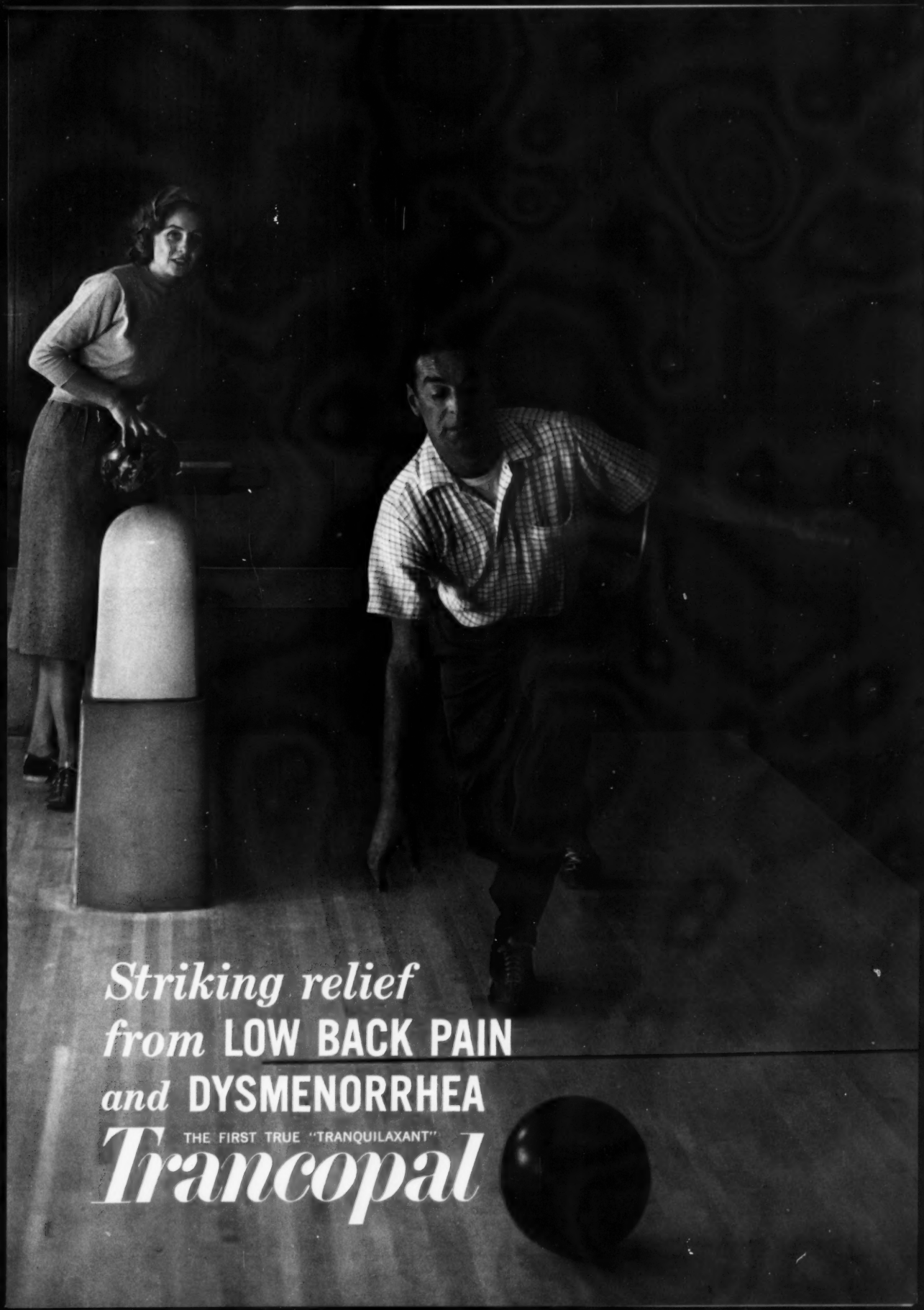
Naturētin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

SQUIBB

Squibb Quality—the Priceless Ingredient

Rx Naturetin 5mg. #30 Disp. Sig: 1 each morning.

'RAUDIXIN'® AND 'NATURETIN' ARE SQUIBB TRADEMARKS.


Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is what you can expect when you prescribe

for dysmenorrhea

and premenstrual tension

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

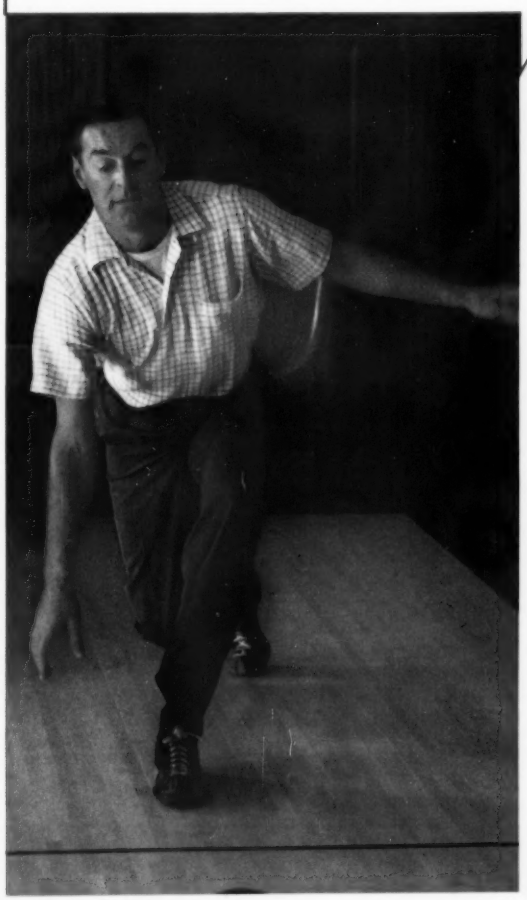
Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain



Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:

Low back pain (lumbago, etc.)
Neck pain (torticollis)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow
Myositis
Postoperative muscle spasm

Psychogenic:

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

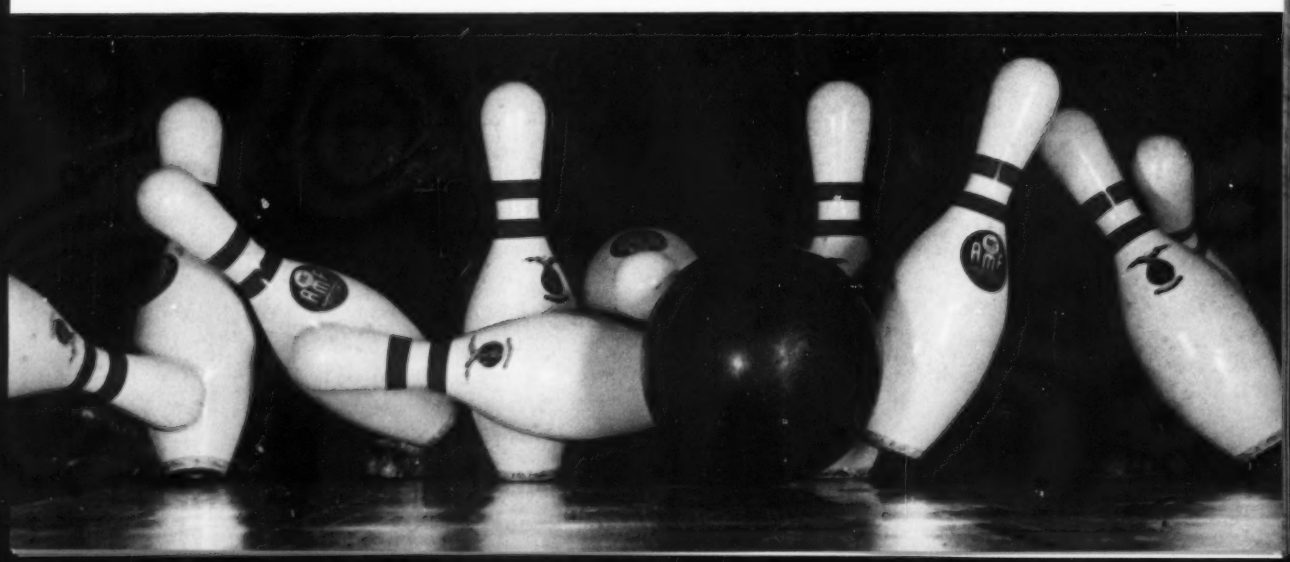
NEW STRENGTH ▶

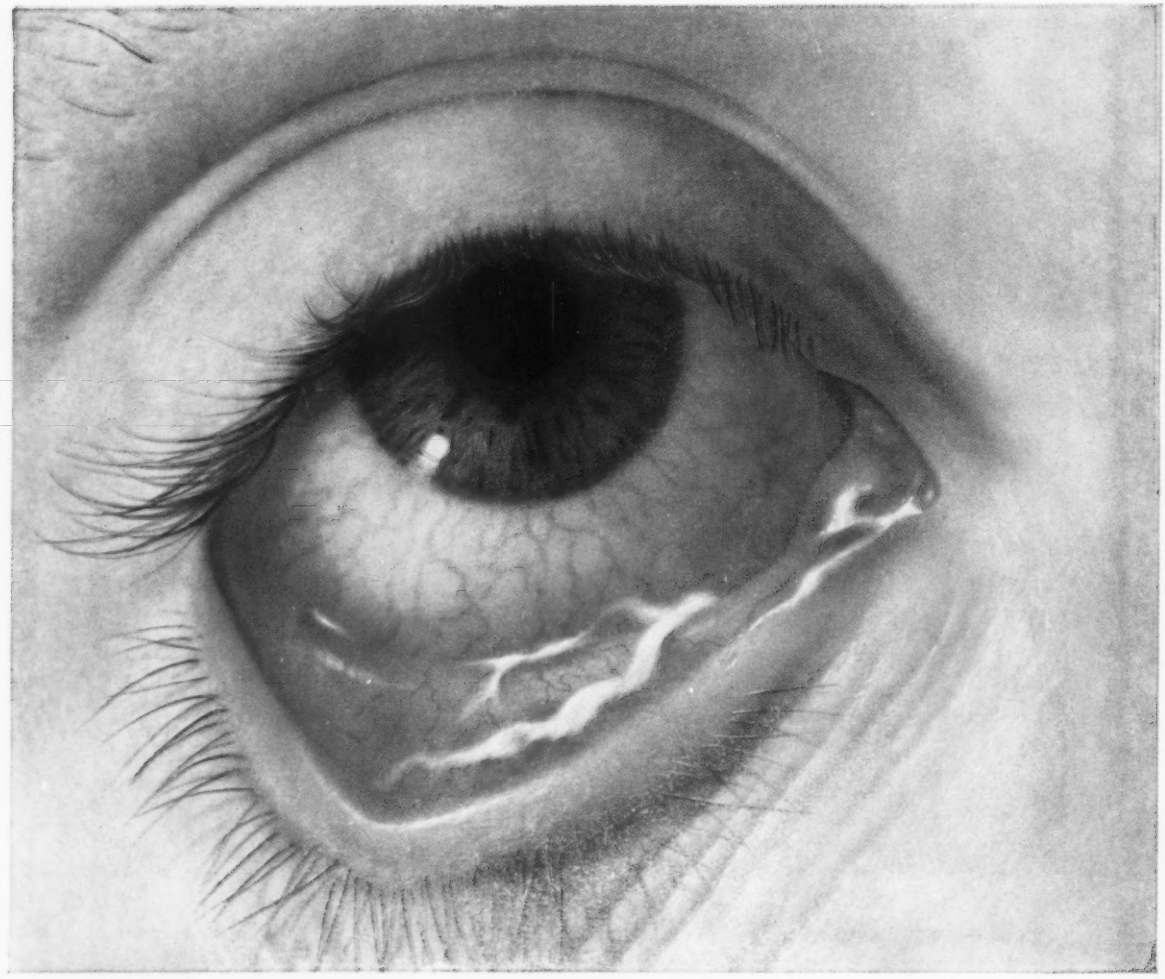
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea; a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.





no irritating crystals[1] · uniform concentration in each drop[2]

STERILE OPHTHALMIC SOLUTION

NEO-HYDELTRASOL®

PREDNISOLONE 21-PHOSPHATE-NEOMYCIN SULFATE

2,000 TIMES MORE SOLUBLE THAN PREDNISOLONE OR HYDROCORTISONE

"The solution of prednisolone has the advantage over the suspension in that no crystalline residue is left in the patient's cul-de-sac or in his lashes . . . . The other advantage is that the patient does not have to shake the drops and is therefore sure of receiving a consistent dosage in each drop."[2]

1. Lippmann, O.: Arch. Ophth. **57**:339, March 1957.
2. Gordon, D.M.: Am. J. Ophth. **46**:740, November 1958.

supplied: 0.5% Sterile Ophthalmic Solution NEO-HYDELTRASOL (with neomycin sulfate) and 0.5% Sterile Ophthalmic Solution HYDELTRASOL®. In 5 cc. and 2.5 cc. dropper vials. Also available as 0.25% Ophthalmic Ointment NEO-HYDELTRASOL (with neomycin sulfate) and 0.25% Ophthalmic Ointment HYDELTRASOL. In 3.5 Gm. tubes.

MSD MERCK SHARP & DOHME Division of Merck & Co., Inc., Philadelphia 1, Pa.

AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE

WHY IS DIABETES IN INFANTS SO DIFFICULT TO DIAGNOSE?

Because of the infrequency of the disease in this age group, its sudden onset, the profusion of inconsistent presenting symptoms, and because the accompanying symptoms of anorexia and vomiting are also characteristic symptoms of many other ills of infancy.

*Source: Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

for those pediatric puzzlers..."A routine urinalysis and blood sugar should be done whenever the possibility of diagnosing diabetes is entertained."*

the standardized urine-sugar test for reliable quantitative estimations

AMES COMPANY, INC. Elkhart, Indiana Toronto, Canada

COLOR-CALIBRATED CLINITEST®

BRAND Reagent Tablets

84060

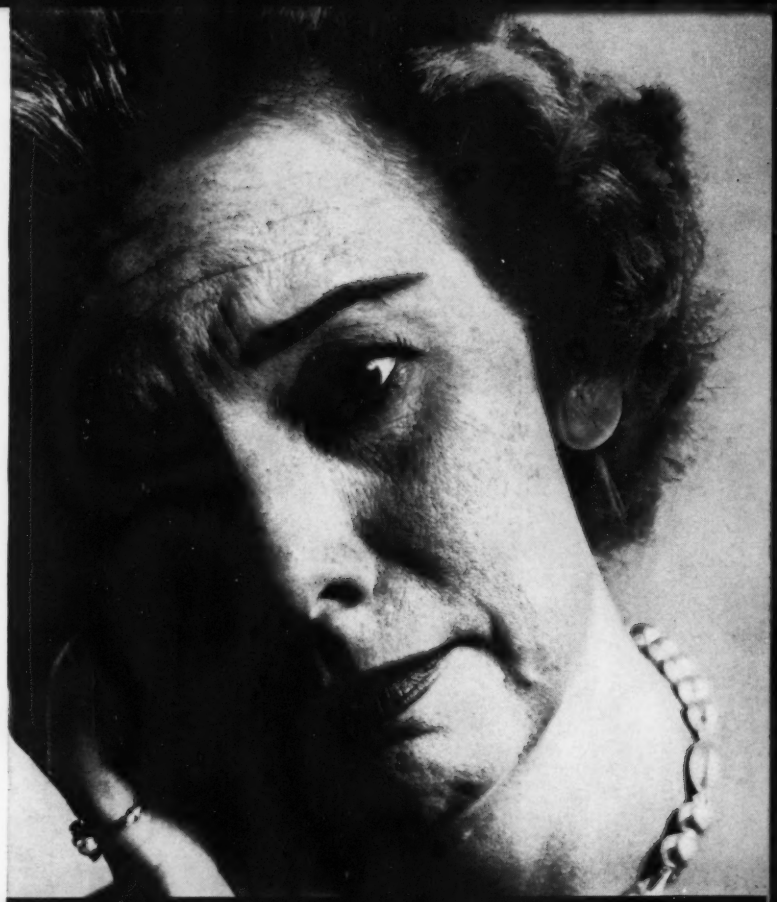
DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

Symptoms	No. of Patients	Per cent of total group
Polyuria	93	84.5
Polydipsia	89	81.0
Weight loss	47	42.7
Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
Boils	1	0.9
Headache	1	0.9
Abdominal cramps	1	0.9

Adapted from Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.*

- **full-color calibration, clear-cut color changes**
- **established "plus" system covers entire critical range**
- **standard blue-to-orange spectrum**
- **standardized, laboratory-controlled color scale**
- **"urine-sugar profile" graph for closer control**



when anxiety takes the form of apathy, listlessness and emotional fatigue

STELAZINE®

brand of trifluoperazine

the unique tranquilizer that relieves anxiety and restores normal drive

- often effective where other agents fail
- fast therapeutic response with very low doses
- side effects infrequent, usually slight and transitory
- convenient b.i.d. administration
- well-accepted by patients

AVAILABLE: For use in everyday practice—1 mg. tablets, in bottles of 50 and 500. USUAL DOSAGE: One 1 mg. tablet, b.i.d. (morning and night). Additional information available on request from Smith Kline & French Laboratories, Philadelphia 1.

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